CHAPTER

62 Intravascular Ultrasound

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KEY POINTS

- Intravascular ultrasound (IVUS) has provided significant insights into biologically mediated processes of the vasculature, such as the extent of plaque burden, vascular remodeling, and restenosis.
- IVUS has proved to be a practically useful tool in the evaluation and guidance of interventional techniques, including balloon angioplasty, debulking techniques, conventional stenting, brachytherapy, and, most recently, drug-eluting stents.
- Improvements in core IVUS technology have allowed for higher-resolution images and greater operator convenience.
- Advanced technical developments currently being explored may further enhance the utility of IVUS in both research and clinical arenas of future interventional cardiology, particularly with sophisticated therapeutic technologies to modify local vascular biology.

Intravascular ultrasound (IVUS) imaging has provided, for the first time, a clinical method to directly visualize atherosclerosis and other pathologic conditions within the walls of blood vessels. Because the ultrasound signal is able to penetrate below the luminal surface, the entire cross-section of an artery—including the complete thickness of a plaque—can be imaged in real time. This offers the opportunity to gather diagnostic information about the process of atherosclerosis and to directly observe the effects of various interventions on the plaque and arterial wall.

The first ultrasound imaging catheter system was developed by Bom and colleagues in Rotterdam in 1971 for intracardiac imaging of chambers and valves.[1,2] In the early to mid-1980s, several groups began work on different catheter systems designed to image plaque and facilitate balloon angioplasty and other catheter-based interventions.[3-7] The first images of human vessels were recorded by Yock and colleagues in 1988,[8] with coronary images produced the next year by the same group[9] and by Hodgson and colleagues.[10] The intervening period has seen rapid technical improvements of the systems, with significant enhancement in image quality and miniaturization of the imaging catheters.

IMAGING SYSTEMS AND PROCEDURES

IVUS imaging systems use reflected sound waves to visualize the vessel wall in a two-dimensional, tomographic format, analogous to a histologic cross-section. These systems use significantly higher frequencies than noninvasive echocardiography, achieving greater radial resolutions at the expense of limited beam penetration. The resolution, depth of penetration, and attenuation of the acoustic pulse by tissue are dependent on the geometric and frequency properties of the transducer. Current IVUS catheters used in the coronary arteries have center frequencies ranging from 20 to 45 MHz, providing theoretical lower limits of resolution (calculated as half the wavelength) of 31 and 19 μm, respectively. In practice, the radial resolution is at least two to five times poorer, determined by factors such as the length of the emitted pulse and the position of the imaged structures relative to the transducer.

Catheter Design and Imaging Procedures

There are two basic catheter designs, based on solid-state or mechanical approaches (Fig. 62-1). Both types of catheters generate a 360-degree, cross-sectional image plane that is perpendicular to the catheter tip.

Solid-State Dynamic Aperture System

In the solid-state approach, the individual elements of a circumferential array of transducer elements mounted near the tip of the catheter are activated with different time delays, to create an ultrasound

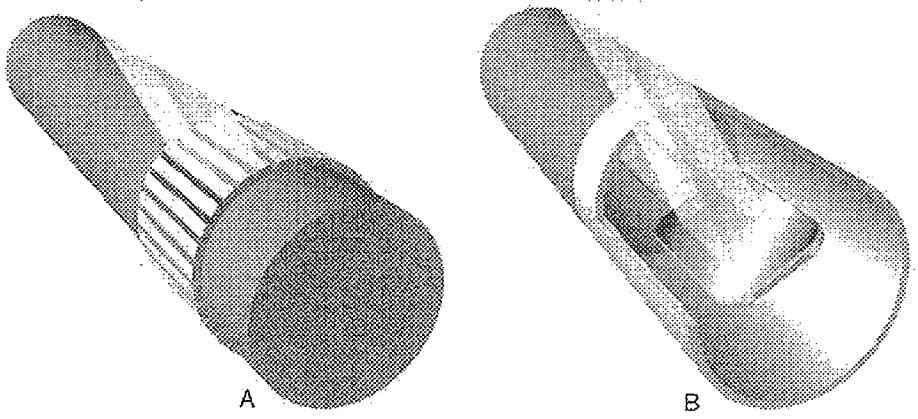

Figure 62-1. Diagrams of the two basic imaging catheter designs, solid state (**A**) and mechanical (**B**).

beam that sweeps the circumference of the vessel. As the number of elements has increased, there have been progressive improvements in lateral resolution. Complex miniaturized integrated circuits in the catheter tip control the timing and integration of the transducer activation and route the resulting echocardiographic information to a computer, where cross-sectional images are reconstructed and displayed in real time. In addition to the absence of any moving parts, one of the advantages of the multielement approach is the ability to manipulate the beam electronically—achieving, for example, the ability to focus at different depths.

The current solid-state coronary catheter system (Volcano Therapeutics, Inc., Rancho Cordova, CA) has 64 transducer elements arranged around the catheter tip and uses a center frequency of 20 MHz. The latest coronary catheters in a rapid-exchange configuration are 2.9 Fr and thus compatible with a 5-Fr guiding catheter. Larger peripheral imaging catheters are produced in both over-the-wire and rapid-exchange configurations. As an exception, a phased-array catheter (8-Fr or 10-Fr) for intracardiac echocardiographic imaging (Siemens Medical Solutions USA, Malvern, PA) uses a different technology, adapted from transesophageal echocardiography, that provides a sector ultrasound image with color and spectral Doppler capabilities. The catheter is compatible with multiple-frequency imaging (5.0 to 10 MHz) so that the operator can determine the desired tradeoff between resolution and penetration (up to 15 cm).

Setup of the solid-state catheter is straightforward: A thin cable connector is passed off the sterile field to attach to a pole-mounted remote unit. This, in turn, is connected to the system cart with a monitor, videotape recorder, and digital storage capacity. Before IVUS imaging, an intravenous injection of 5,000 to 10,000 U heparin or equivalent anticoagulation should be administered, as well as intracoronary nitroglycerine (100 to 300 μg), to reduce the potential for spasm. Because the solid-state transducer has a zone of "ring-down artifact" encircling the catheter, an extra step is required to form a mask of the artifact and subtract this from the image. The mask is usually acquired by disengaging the guiding catheter from the ostium and positioning the tip of the imaging catheter free in the aorta. The imaging element is then advanced distal to the area of interest, and the length of the target vessel is scanned by a motorized or manual withdrawal of the entire catheter over a standard 0.014-inch angioplasty guide wire.

Mechanically Rotating Single-Transducer System

In the mechanical approach, a single transducer element is rotated inside the tip of a catheter via a flexible torque cable spun by an external motor drive unit attached to the proximal end of the catheter. Images from each angular position of the transducer are collected by a computerized image array processor, which synthesizes a cross-sectional ultrasound image of the vessel.

The mechanical IVUS system is available commercially from two manufacturers in the United States and one in Japan. The imaging catheters use a 40- or 45-MHz transducer with a distal crossing profile of 3.2 Fr (compatible with 6-Fr guiding catheters). Larger catheters with lower center frequencies are also available for peripheral and intracardiac echocardiographic imaging. The catheters are advanced over a standard guide wire using a short rail section at the catheter tip. The length of the target vessel is scanned by retracting the rotating transducer manually or mechanically within a stationary outer sheath at the distal end of the catheter (Boston Scientific

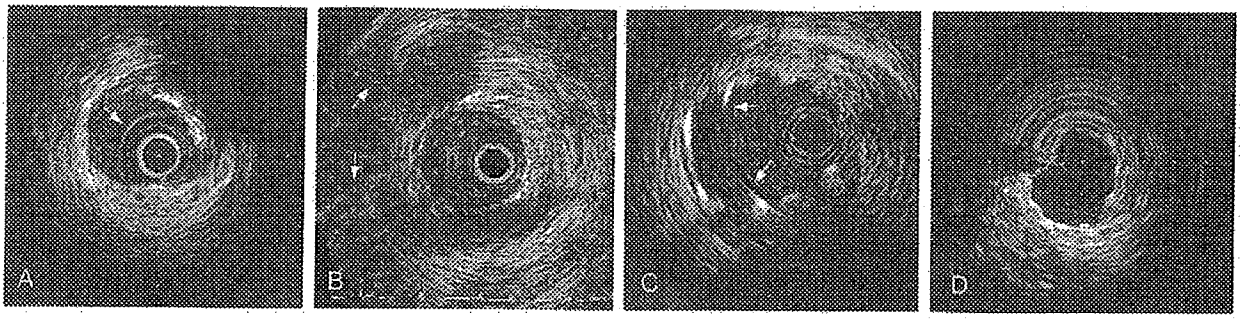

Figure 62-2. Common image artifacts. **A,** A "halo" or a series of bright rings immediately around the mechanical intravascular ultrasound (IVUS) catheter (*arrow*) is usually caused by air bubbles that need to be flushed out. **B,** Radiofrequency noise (*arrows*) appears as alternating radial spokes or random white dots in the far-field. The interference is usually caused by other electrical equipment in the catheterization laboratory. **C,** "White cap" artifacts caused by side lobe echoes (*arrows*) originate from a strong reflecting surface, such as metal stent struts or calcification. The smearing of the strut image can lead to the mistaken impression that the struts are protruding into the lumen, potentially interfering with area measurements and the assessment of apposition, dissection, and so on. **D,** Non-uniform rotational distortion (NURD) results in a wedge-shaped, smeared appearance in one or more segments of the image (between 9 and 4 o'clock in this example).

Corporation, Natick, MA; Volcano Therapeutics) or by moving the catheter itself (Terumo Corporation, Tokyo, Japan). The fact that the guide wire runs outside the catheter, parallel to the imaging segment, results in a shadow artifact in the image (the so-called guide wire artifact).

Use of mechanical catheters is similar to the use of solid-state catheters, except that mechanical catheters require flushing with saline before insertion to eliminate any air in the path of the beam. Incomplete flushing can leave microbubbles adjacent to the transducer, resulting in poor image quality once the catheter is inserted (Fig. 62-2). Non-uniform rotational distortion (NURD) can occur when bending of the drive cable interferes with uniform transducer rotation, causing a wedge-shaped, smeared image to appear in one or more segments of the image. This may be corrected by straightening the catheter and motor drive assembly, lessening tension on the guiding catheter, or loosening the hemostatic valve of the Y-adapter.

Head-to-Head Comparisons

Mechanical transducers have traditionally offered advantages in image quality compared with the solid-state systems, although this gap has narrowed in recent years. In general, mechanical catheters have excellent near-field resolution and do not require the subtraction of a mask. At the procedure, the short rail design of the mechanical systems may not track as well as the longer rapid-exchange, solid-state catheter. On the other hand, mechanical catheters with a stationary outer sheath are easy to use with a motorized pullback device, allowing the transducer to be moved through a segment of interest in a precise and controlled manner. The use of motorized pullback is important for two reasons: it gives the ability to measure the length of a given segment or register the position of a given cross-section for repeat studies,[11] and it provides the potential for a reasonably accurate longitudinal or three-dimensional representation of a segment. With both systems, still frames and video images can be digitally archived on local storage memory or a remote server using Digital Imaging and Communications in Medicine (DICOM) Standard 3.0.

IMAGE INTERPRETATION

Three-Layered Appearance of Arterial Wall

The interpretation of IVUS images relies on the fact that the layers of a diseased arterial wall can be identified separately. Particularly in muscular arteries, such as the coronary tree, the media of the vessel stands out as a dark band compared with the intima and adventitia (Fig. 62-3).[12,13] Media are less distinctly seen by IVUS in elastic arteries such as the aorta and carotid, so differentiation of the layers in those vessels can be problematic.[14] However, most of the vessels currently treated by catheter techniques are muscular or transitional, and identification of the medial layer is usually possible (this includes the coronary, iliofemoral, renal, and popliteal systems).

The relative echolucency of media compared with intima and adventitia gives rise to a three-layered appearance (bright-dark-bright), first described in vitro by Meyer and colleagues[15] and subsequently confirmed in vivo.[16] The lower ultrasound reflectance of the media is due to the presence of less collagen and elastin than in the neighboring layers. Because the intimal layer reflects ultrasound more strongly than the media, a spillover effect, known as "blooming," is seen in the image. This results in a slight overestimation of the thickness of the intima and a corresponding underestimation of the medial thickness. On the other hand, the media/adventitia border

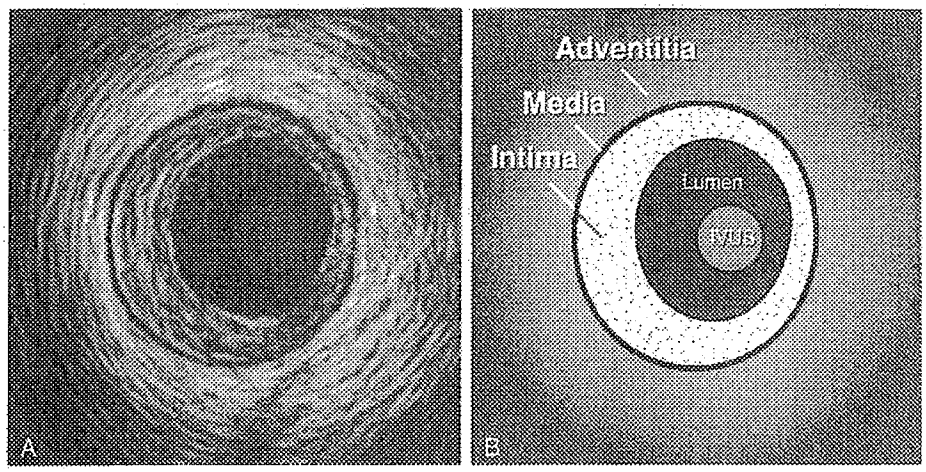

Figure 62-3. Intravascular ultrasound (IVUS) image **(A)** and schematic diagram **(B)** demonstrate the classic three-layered appearance of intima (plaque), media, and adventitia. In many cases, the media can be difficult to resolve clearly in some portion of the image, but in this particular image, it stands out in all sectors. Note the speckled appearance of the blood within the lumen, particularly near the luminal border.

is accurately rendered, because a step-up in echo reflectivity occurs at this boundary and no blooming appears. The adventitia and periadventitial tissues are similar enough in echoreflectivity that a clear outer adventitial border cannot be defined.

Several deviations from the classic three-layered appearance are encountered in practice. In truly normal coronary arteries from young patients, echoreflectivity of the intima and internal lamina may not be sufficient to resolve a clear inner layer.[17] This is particularly true when the media has a relatively high content of elastin.[18] However, most adults seen in the cardiac catheterization laboratory have enough intimal thickening to show a three-layered appearance, even in angiographically normal segments (Fig. 62-4). At the other end of the spectrum, patients with a significant plaque burden have thinning of the media underlying the plaque,[5,19,20] often to the degree that the media is indistinct or undetectable in at least some part of the IVUS cross-section. This problem is exacerbated by the blooming phenomenon. Even in these cases, however, the inner adventitial boundary (at the level of the external elastic lamina) is always clearly defined. For this reason, most IVUS studies measure and report the plaque-plus-media area as a surrogate measure for plaque area alone. Adding in the media represents only a tiny percentage increase of the total area of the plaque.

Unlike coronary angiograms, IVUS images have an intrinsic distance calibration, which is usually displayed as a grid on the image. Electronic caliper (diameter) and tracing (area) measurements can be performed at the tightest cross-section, as well as at

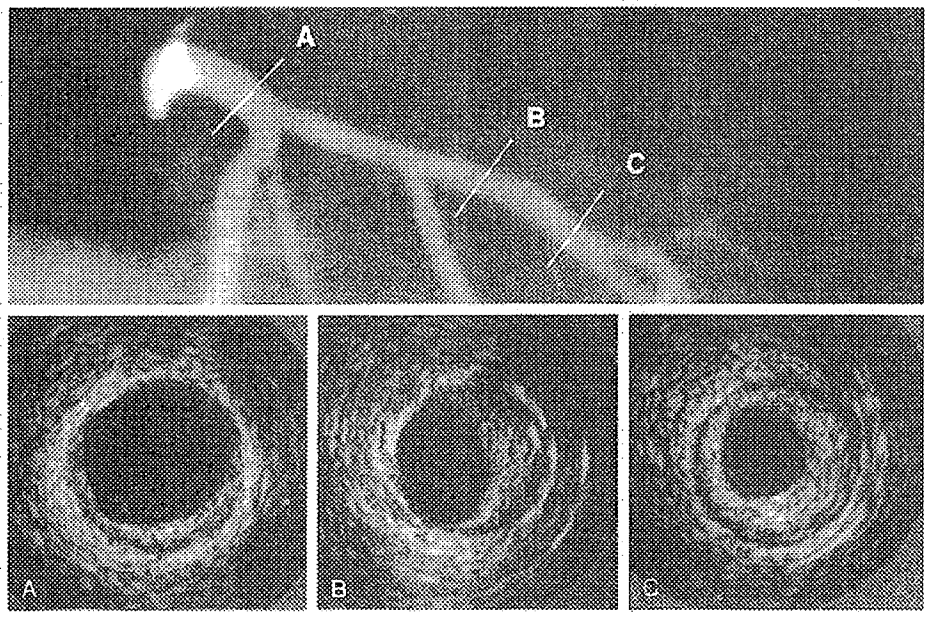

Figure 62-4. Intravascular ultrasound (IVUS) images from a transplantation patient with an almost normal-appearing angiogram *(top)*. **A,** The IVUS image from the left main coronary artery (cross-section A on the angiogram) shows minimal plaque accumulation between 2 and 9 o'clock. **B,** In the left anterior descending coronary artery, the IVUS image shows an eccentric plaque between 12 and 6 o'clock that is not evident on the angiogram (cross-section B). **C,** The image from cross-section C on the angiogram shows a more concentric plaque that also is angiographically undetected.

reference segments located proximal and distal to the lesion.[21] In general, the reference segment is selected as the most normal-looking cross-section (i.e., largest lumen with smallest plaque burden) occurring within 10 mm of the lesion with no intervening major side branches.

Vessel and lumen diameter measurements are important in everyday clinical practice, where accurate sizing of devices is needed. The maximum and minimum diameters (i.e., the major and minor axes of an elliptical cross-section) are the most widely used dimensions. The ratio of maximum to minimum diameter defines a measure of symmetry. Area measurements are performed with computer planimetry; lumen area is determined by tracing the leading edge of the blood/intima border, whereas vessel (or external elastic membrane [EEM]) area is defined as the area enclosed by the outermost interface between media and adventitia. Plaque area (or plaque-plus-media area) is calculated as the difference between the vessel and lumen areas; the ratio of plaque to vessel area is termed percent plaque area, plaque burden, or percent cross-sectional narrowing. With the use of motorized pullback, area measurements can be added to calculate volumes using Simpson's rule.

Plaque Composition

In addition to demonstrating the extent and distribution of plaque within the vessel wall, IVUS provides information about the composition of plaque.[22,23] Regions of calcification are very brightly echoreflective and create a dense shadow more peripherally from the catheter (Fig. 62-5).[5,24-26] Shadowing prevents determination of the true thickness of a calcific deposit and precludes visualization of structures in the tissue beyond the calcium. Another characteristic finding with calcification is reverberation, which causes the appearance of multiple ghost images of the leading calcium interface, spaced at regular intervals radially (see Fig. 62-5C). Like calcium, densely fibrotic tissue gives a bright appearance on the ultrasound scan and can cause shadowing. The brightness is less intense, however, and the beam penetrates a short distance into the tissue beyond the initial interface. The extent of shadowing depends on both the thickness and the density of the fibrotic region as well as the transducer strength. Fatty plaque is less echogenic than fibrous plaque. The brightness of the adventitia can be used as a gauge to discriminate predominantly fatty from fibrous plaque. An area of plaque that images darker than the adventitia is fatty. In an image of extremely good quality, the presence of a lipid pool can be inferred from the appearance of a dark region within the plaque.[5,7] However, not all hypoechoic zones within plaque represent lipid. False channels within the plaque can give a similar appearance, and, occasionally, shadowing from an adjacent region of calcification or fibrosis may look much like a lipid pool.[27]

One of the major limitations of IVUS in terms of identifying tissue is the difficulty in discriminating thrombus from soft plaque.[28] This is a complementary strength for angioscopy, whose color capability makes identification of thrombus at the luminal surface relatively easy. On ultrasound scanning, clues to the presence of thrombus are useful in some cases. Fresh thrombus can exhibit a scintillating tissue appearance that is fairly characteristic. Thrombus is much more likely than soft plaque to have the appearance of clefts or microchannels. In favorable cases, a thrombus has an undulating motion during the pulse cycle that is not seen with plaque. Computer-enhanced processing of the raw ultrasound signal promises to help in the discrimination between thrombus and plaque.[29-33]

Image Orientation

One important aspect of image interpretation is determining the position of the imaging plane within the artery. The IVUS beam penetrates beyond the artery, providing images of perivascular structures, including the cardiac veins, myocardium, and pericardium.[34] These structures have a characteristic

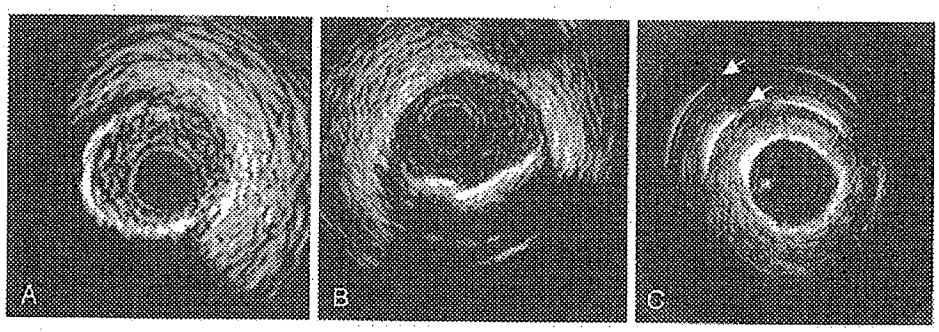

Figure 62-5. Examples of coronary calcification. **A,** A rim of calcium is seen between 5 and 10 o'clock, located beneath a fibrofatty plaque that tightly surrounds the catheter. Note the shadowing beyond the calcium. **B,** Superficial calcium (between 3 and 7 o'clock) at the luminal surface. The speckles within the lumen are signals from blood. **C,** Circumferential, "napkin ring" calcification. Two arcs of reverberation are seen *(arrows)*, and another pair of reverberations is seen to the right of the arrows. The small bright point adjacent to the catheter at 8:30 o'clock is the guide wire artifact from this mechanical catheter.

with a resulting restenosis rate of 21%.[108] These findings were confirmed in the contemporary series of the Stent versus Directional Coronary Atherectomy Randomized Trial (START).[109] When considered together, these studies suggest that a technique that could effectively remove relatively large amounts of plaque (with a residual of 50% or less) would have restenosis rates that are competitive with stenting. The ABACAS trial also provided some new insight into the impact of deep wall cutting (i.e., cutting into media or adventitia) on restenosis.[110] Segments with deep wall cuts on average had *lower* rates of recurrence than did lesions without deep wall invasion. However, some of the patients with subintimal cuts had local aneurysm formation.

IVUS studies after atherectomy and angioplasty have provided some other key insights into the mechanisms of restenosis. In addition to intimal proliferation, there is a second major process causing late lumen loss: shrinkage of the treated segment (Fig. 62-9), which is a form of remodeling similar to the process illustrated in Figure 62-7B.[111-114] By performing serial IVUS examinations at multiple intervals after DCA, Kimura and colleagues demonstrated that, overall, more than 60% of lumen loss at 6 months was caused by shrinkage, with the remainder caused by intimal proliferation.[114] It is unclear which factors may predispose a treated segment to restenosis, although remodeling, seen as an important mechanism of restenosis, has opened a new line of investigation into molecular mechanisms and potential therapies. Clearly, the shrinkage process is directly preventable by stenting. This probably accounts for the favorable restenosis rates seen with this technique, despite even greater degrees of intimal proliferation than with non-stent interventions.[112] A recent study of intracoronary radiation therapy (ICRT) also showed beneficial effects on remodeling at non-stented lesions.[115]

Bare Metal Stents

Insights into Mechanism of Action

Stent struts are easily visualized on IVUS examination as a collection of bright, distinct echoes, characteristic for each stent type. In contrast, the proliferative tissue within the stent struts has low echoreflectivity, similar to thrombus, so that optimal instrument settings are required to visualize the restenotic material clearly. Stents essentially provide a rigid scaffold against the force of vessel recoil. During stent implantation, axial extrusion of noncalcified plaque into the adjacent reference zones can occur (Fig. 62-10).[116-119] Mintz and colleagues demonstrated a similar phenomenon in balloon angioplasty.[120] However, the extrusion effect in stenting may be more prominent than for balloon angioplasty, commensurate with the increased ability of the stent to enlarge and hold open the treated segment. Extrusion of plaque may also contribute to the step-up/step-down appearance seen on angiography, as well as some of the side branch encroachment after stent deployment.

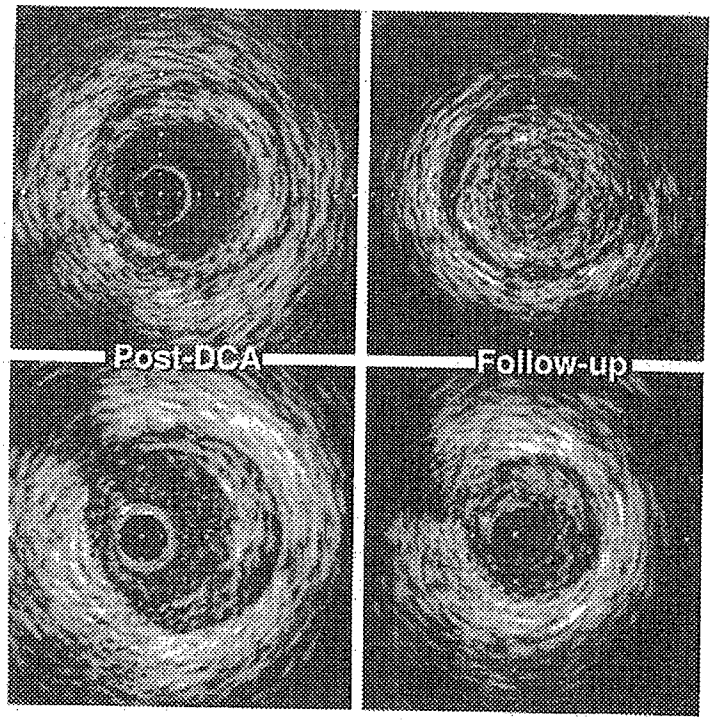

Figure 62-9. Two different mechanisms of restenosis as demonstrated by serial IVUS after non-stent intervention. *Top,* Extensive plaque proliferation leading to late lumen loss without a substantial change in the overall (media-to-media) dimensions of the vessel. *Bottom,* Negative remodeling or shrinkage is the major contributor to lumen loss.

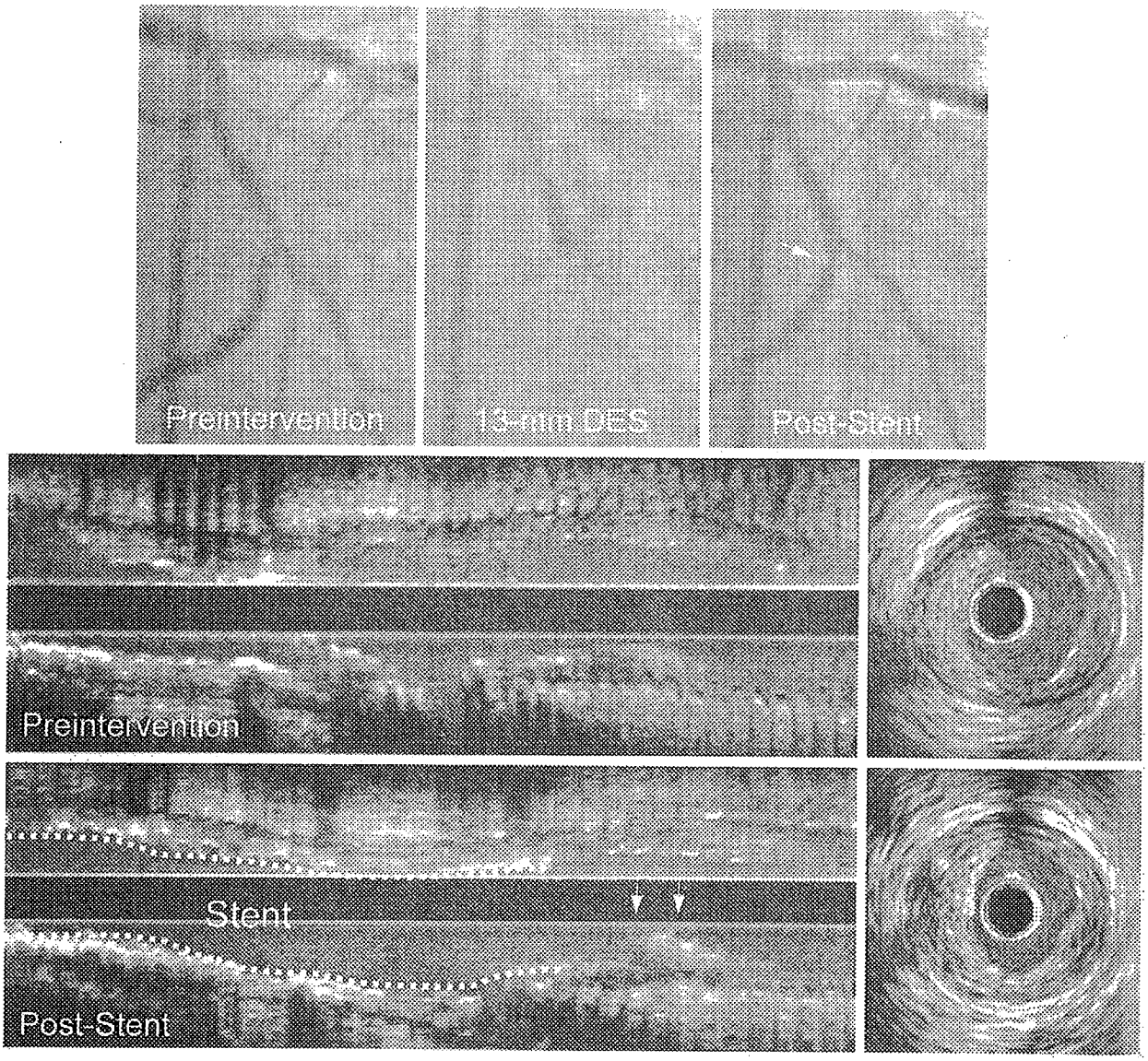

Figure 62-10. Plaque extrusion occurring as a result of stenting. The coronary angiogram taken immediately after stenting showed a new stenosis *(arrow)* at the distal adjacent segment to the implanted stent. Although spasm, dissection, and/or hematoma was suspected by angiography, intravascular ultrasound (IVUS) revealed that the secondary lesion was caused by a significant plaque increase *(arrows)*, presumably resulting from axial plaque redistribution, otherwise known as "plaque shift" from the stented segment into this region.

Guidance of Procedures

IVUS has identified several stent deployment issues, including incomplete expansion and incomplete apposition (Fig. 62-11). Incomplete expansion occurs when a portion of the stent is inadequately expanded compared with the distal and proximal reference dimensions, as may occur where dense fibrocalcific plaque is present. Incomplete apposition (seen in 3% to 15% of stent cases) occurs when part of the stent structure is not fully in contact with the vessel wall, possibly increasing local flow disturbances and the potential risk for subacute thrombosis in certain clinical settings. The collaboration of Tobis and Colombo in the early 1990s demonstrated an unexpectedly high percentage of these stent deployment issues, leading to their development of the current high-pressure stent deployment techniques.[121,122]

After stent implantation, tears at the edge of the stent (marginal tears or pocket flaps) occur in 10% to 15% of cases (see Fig. 62-11).[123-125] These tears have been attributed to the shear forces created at the junction between the metal edge of the stent and the adjacent, more compliant tissue, or to the effect of balloon expansion beyond the edge of the stent (the "dog-bone" phenomenon). Although minor

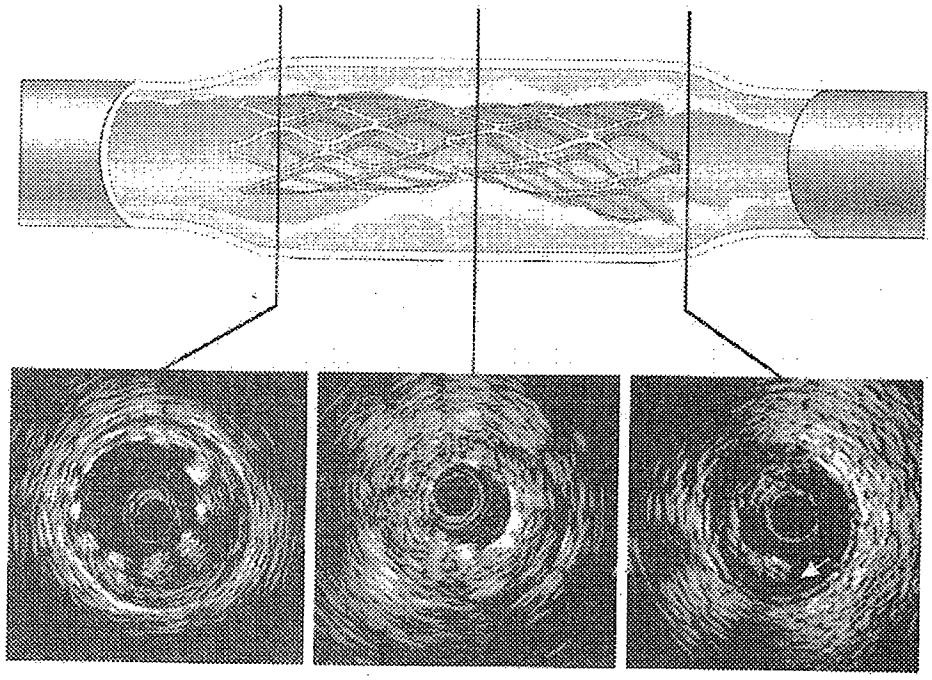

Figure 62-11. Problems with stent deployment detected by intravascular ultrasound (IVUS). The diagram indicates the cross-sections shown in the IVUS images. *Left,* Incomplete apposition, in which there is a gap between a portion of the stent and the vessel wall (between 12 and 7 o'clock on the IVUS image). The apparent thickness of the stent struts in this area is due to reverberations. *Middle,* Incomplete expansion relative to the ends of the stent and the reference segments. *Right,* An edge tear or "pocket flap" with a disruption of plaque at the stent margin *(arrow)*.

non-flow-limiting edge dissections may not be associated with late angiographic in-stent restenosis, significant residual dissections can lead to an increased risk of early major adverse cardiac events.[126,127] The current practice in our laboratory is to make a determination from the IVUS image as to whether the tear appears to be flow-limiting (i.e., whether there is an extensive tissue arm projecting into the lumen). If this is the case, an additional stent is placed to cover this region.

Over the past decade, a number of studies have shown that IVUS-guided stent placement improves the clinical outcome of bare metal stents.[128-137] In the Multicenter Ultrasound-guided Stent Implantation in Coronaries (MUSIC) trial, IVUS-guided stenting required: (1) complete apposition over the entire stent length; (2) in-stent minimum stent area (MSA) greater than or equal to 90% of the average of the reference areas or 100% of the smallest reference area; and (3) symmetric stent expansion with the minimum/maximum lumen diameter ratio greater than or equal to 0.7.[138] Subacute thrombosis of less than 2% was believed to represent a reduction compared with nonguided deployment, although, with current antiplatelet regimens, similar results can usually be achieved by high-pressure postdilation without IVUS confirmation. Nevertheless, a number of studies have suggested a link between suboptimal stent implantation and stent thrombosis, including the Predictors and Outcomes of Stent Thrombosis (POST) registry, which demonstrated that 90% of thrombosis patients had suboptimal IVUS results (incomplete apposition, 47%; incomplete expansion, 52%; and evidence of thrombus, 24%), even though only 25% of patients had abnormalities on angiography.[139] These observations were replicated in a more recent study by Cheneau and colleagues, which suggested that mechanical factors continue to contribute to stent thrombosis, even in this modern stent era, with optimized antiplatelet regimens.[140] Although the use of IVUS in all patients for the sole purpose of reducing thrombosis is clearly not warranted from a cost standpoint, IVUS imaging should be considered in patients who are at particularly high risk for thrombosis (e.g., slow flow) or in whom the consequences of thrombosis would be severe (e.g., left main coronary artery or equivalent).

MSA, as measured by IVUS, is one of the strongest predictors for both angiographic and clinical restenosis after bare metal stenting.[66,141-144] Kasaoka and colleagues indicated that the predicted risk of restenosis decreases 19% for every 1-mm^2 increase in MSA and suggested that stents with MSA greater than 9 mm^2 have a greatly reduced risk of restenosis.[143] In the Can Routine Ultrasound Improve Stent Expansion (CRUISE) trial, IVUS guidance by operator preferences increased MSA from 6.25 to 7.14 mm^2, leading to a 44% relative reduction in target vessel revascularization at 9 months, compared with angiographic guidance alone.[133] In the Angiography versus IVUS-Directed stent placement (AVID) trial, IVUS-guided stent implantation resulted in larger acute dimensions than angiography alone (7.54 versus 6.94 mm^2), without an increase in complications, and lower 12-month target lesion revascularization rates for vessels with angiographic reference diameter less than 3.25 mm, severe stenosis at preintervention (>70% angiographic diameter stenosis), and vein grafts.[132] However, controversial results were also reported in some IVUS-guided stent trials,[145,146] presumably due

to differing procedural end points for IVUS-guided stenting, as well as various adjunctive treatment strategies that were used in these trials in response to suboptimal results (Table 62-1). Overall, a meta-analysis of 9 clinical studies (2972 patients) demonstrated that IVUS-guided stenting significantly lowers 6-month angiographic restenosis (odds ratio [OR] = 0.75, 95% confidence interval [CI], 0.60 to 0.94; P = .01) and target vessel revascularizations (OR = 0.62; 95% CI, 0.49 to 0.78; P = .00003), with a neutral effect on death and nonfatal myocardial infarction, compared to an angiographic optimization.[147]

Insights into Long-Term Outcomes

In-stent restenosis is primarily caused by intimal proliferation rather than chronic stent recoil.[112,148] Growth of neointima is usually greatest in the areas with the largest plaque burden,[64,149,150] and the intimal growth process seems to be more aggressive in diabetic patients.[151] In the treatment of in-stent restenosis, IVUS can be helpful to differentiate pure intimal ingrowth from poor stent expansion, especially if ablative therapies are being considered. Using serial IVUS immediately before and after balloon angioplasty for in-stent restenosis, Castagna and colleagues[152] showed, in 1090 consecutive in-stent restenosis lesions, that 38% of lesions had an MSA of less than 6.0 mm^2. Stent underexpansion can result in clinically significant lumen compromise even with minimal neointimal hyperplasia. For this type of in-stent restenosis, mechanical optimization is appropriate in most cases.

IVUS can also track the response to treatment, with evidence that angioplasty of in-stent restenosis

Table 62-1. IVUS Versus Angiographic Guidance of Bare Metal Stent Implantation

Study* (Ref. No.)	N	Population	Study Design	IVUS Criteria for Optimal Expansion	Criteria Fulfilled	End Points	Results
Albiero et al. (128)	312	De novo, native	Multicenter, registry	Complete apposition, no ref disease, MSA ≥60% of average ref VA (early phase) or MSA ≥ distal ref LA (late phase)	NA	6-mo angiography	IVUS better (early phase)
Blasini et al. (129)	212	De novo and restenotic, native and SVG	Single center, registry	Complete apposition, no residual dissection, MSA >8 mm^2 and/or 90% of average ref LA	50%	6-mo angiography	IVUS better
Choi et al. (130)	278	De novo, native	Single center, registry	Complete apposition, no residual dissection, MSA ≥80% of distal ref LA	NA	Acute closure, 6-mo MACE	IVUS better
Gaster et al. (131)	108	De novo and restenotic, native	Single center, randomized	MUSIC criteria	64%	6-mo angiography, CFR, FFR, TVR; 2.5-yr MACE	IVUS better
AVID (132)	759	De novo, native and SVG	Multicenter, randomized	MUSIC criteria	NA	12-mo TLR	IVUS better (subset analysis)
CRUISE (133)	499	De novo and restenotic, native	Multicenter, nonrandomized	Discretion of individual institutional practice	—	9-mo TVR	IVUS better
OPTICUS (145)	550	De novo and restenotic, native	Multicenter, randomized	MUSIC criteria	56%	6-mo angiography, 12-mo MACE	No difference
PRESTO (146)	9070	De novo and restenotic, native	Multicenter, nonrandomized	Discretion of individual institutional practice	—	9-mo MACE	No difference
RESIST (134, 135)	155	De novo, native	Multicenter, randomized	MSA >80% of average ref LA	80%	6-mo angiography, 18-mo MACE	IVUS better (nonsignificant reduction)
SIPS (136)	269	De novo and restenotic, native	Single center, randomized	MLA >65% of average ref LA	69%	6-mo angiography, 2-yr TLR	IVUS better (2-year TLR)
TULIP (137)	144	Long lesions (>20 mm)	Single center, randomized	Complete apposition, MLD ≥80% of average ref diameter, MSA ≥ distal ref LA	89%	6-mo angiography, 12-mo MACE	IVUS better

*AVID, Angiography versus IVUS-Directed stent placement trial; CRUISE, Can Routine Ultrasound Influence Stent Expansion study; MUSIC, Multicenter Ultrasound guided Stent Implantation in Coronaries; OPTICUS, Optimization with ICUS to Reduce Stent Restenosis; PRESTO, Results of Prevention of REStenosis with Tranilast and its Outcomes Trial; RESIST, REStenosis after Intravascular ultrasound STenting; SIPS, Strategy for IVUS-Guided PTCA and Stenting; TULIP, Thrombocyte activity evaluation and effects of Ultrasound guidance in Long Intracoronary Stent Placement.
CFR, coronary flow reserve; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LA, lumen area; MACE, major adverse cardiac events; MLD, minimum lumen diameter; MSA, minimum stent area; ref, reference vessel; SVG, saphenous vein graft; TLR, target lesion revascularization; TVR, target vessel revascularization; VA, vessel area.

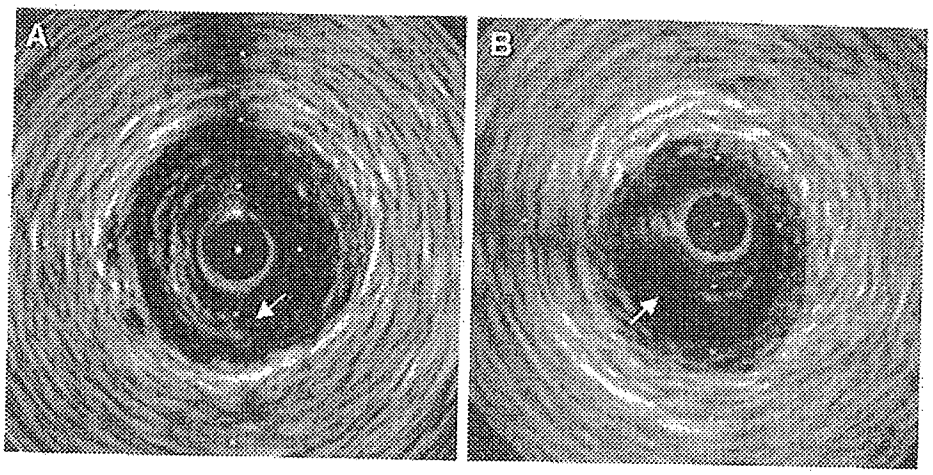

Figure 62-12. Arrows indicate unhealed dissection (A) and echolucent neointimal tissue, so-called acoustic hole or "black hole" (B), observed at follow-up after intracoronary radiation therapy.

is followed by early lumen loss due to decompression[153] and/or reintrusion[154] of tissue immediately after intervention. This phenomenon was more prominent in longer lesions and in those with greater in-stent tissue burden, which may partially account for the worse long-term outcomes in diffuse versus focal in-stent restenosis. Direct tissue removal, rather than tissue compression/extrusion through the stent struts, may help minimize early lumen loss due to this phenomenon. Several investigators have reported a considerable reduction in angiographic and/or clinical recurrence of in-stent restenosis in patients with diffuse in-stent restenosis treated with ablative therapies (DCA, rotational atherectomy, or laser angioplasty) compared with PTCA alone.[155-161]

Intracoronary Radiation Therapy

Insights into Mechanism of Action

ICRT, the first biologic treatment targeting excessive proliferative response of vascular smooth muscle cells to mechanical intervention, has undergone extensive clinical testing with IVUS characterization. Regardless of radiation source or delivery platform, most IVUS studies of ICRT in PTCA, stenting, and treatment of in-stent restenosis showed significant in-lesion or in-stent efficacy.[162-171] Serial IVUS investigations confirmed that these beneficial effects are primarily derived from decreased neointimal hyperplasia, but there is also an effect from accelerated positive remodeling at the irradiated segment.[115,162]

Guidance of Procedures

IVUS revealed that a combination of increased neointimal hyperplasia and either absence of positive remodeling or negative remodeling accounts for the unfavorable edge effect of ICRT.[172-174] Because, in catheter-based ICRT (not radioactive stents), most edge effects are related to inadequate coverage of injured edge segments (so-called geographic miss),[175] IVUS guidance may greatly enhance the safety and efficacy of this highly geographically specific technique. A combined ICRT/imaging device was developed to facilitate the fine-tuning of catheter positioning.[176] This device also forms an asymmetric dose distribution to compensate for the eccentricity of the target plaque as well as the off-center position of the catheter in response to on-line IVUS guidance. Other investigator groups have developed detailed dosimetric analysis algorithms, based on dose-volume histograms derived from three-dimensional IVUS,[177-183] for optimal dose prescription.

Insights into Long-Term Outcomes

Unusual IVUS observations related to ICRT include unhealed dissections, late-acquired incomplete stent apposition, and acoustic holes (or "black holes")—that is, echolucent neointimal tissue. Delayed healing is commonly seen after brachytherapy in general. A substudy from the Beta Energy Restenosis Trial (BERT) reported that 8 (50%) of 16 dissections identified immediately after PTCA were still present at 6-month follow-up.[184] Similarly, an IVUS analysis from the Stents and Radiation Therapy (START) 40/20 trial showed that 43% of dissections had partially healed and 7% were unchanged over time (Fig. 62-12A).[185] Of note, previous nonradiation trials indicated that dissections seen after intervention normally heal within a 6-month follow-up period.[186-188] Late-acquired incomplete stent apposition was reported with both catheter-based ICRT (beta and gamma radiation) and radioactive stents (Fig. 62-13). Detailed serial IVUS examination revealed that this phenomenon is a result of excessive positive remodeling of the underlying vessel wall combined with significant neointimal inhibition.[189,190] Okura and colleagues also reported that late-acquired incomplete stent apposition appears to occur in segments with relatively little peri-stent plaque burden but high radiation dose exposure.[190] Late-acquired incomplete stent apposition can also be seen after mechanical vessel injury in nonradiation interventions (e.g.,

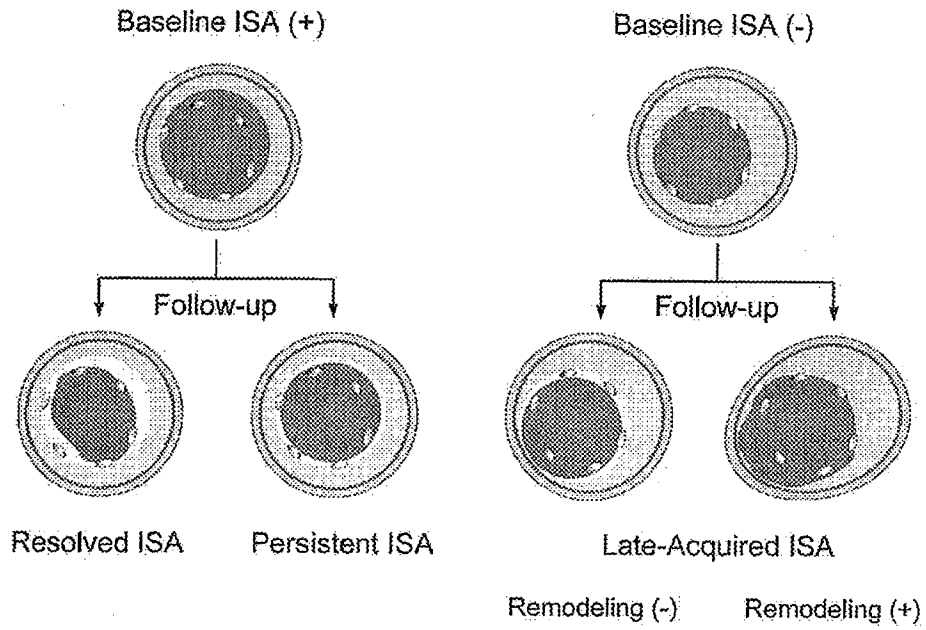

Figure 62-13. Classification of incomplete stent apposition (ISA). Baseline ISA can either be resolved (resolved ISA) or remain (persistent ISA) at follow-up. Late-acquired ISA without vessel expansion is typically seen in thrombus-containing lesions, whereas late-acquired ISA with focal, positive vessel remodeling is more characteristic with brachytherapy and drug-eluting stents.

atherectomy plus stenting),[191] although delayed endothelialization by ICRT may lead to different clinical implications. The acoustic hole or "black hole" consists of echolucent neointimal tissue and has been seen in all types of ICRT (see Fig. 62-12B).[192] Post-ICRT specimens retrieved with DCA show large myxoid areas, with interspersed smooth muscle cells, scattered in a proteoglycan-containing extracellular matrix—findings that are compatible with a weak backscattering of echoes and a dark appearance on IVUS. These IVUS findings after ICRT are unique, but their exact clinical implications remain unknown.

Drug-Eluting Stents

Insights into Mechanism of Action

IVUS observations from the clinical experience with antiproliferative drug-eluting stents (DES) have shown a striking inhibition of in-stent neointimal hyperplasia, whereas the mechanical performances of these new stents are similar to those of conventional bare metal stents.[193-197] Additionally, both statistical and geographic distributions of neointimal hyperplasia can be significantly different between the biologic (DES) and mechanical (bare metal) stents. In general, neointimal volume (as a percentage of stent volume) within bare metal stents follows a near-Gaussian or normal frequency distribution, with a mean value of 30% to 35%. The standard deviation of this statistical distribution represents biologic variability in vascular response to acute and chronic vessel injury by interventions. In contrast, biologic modifications by DES often result in a non-Gaussian frequency distribution, with variable degrees of the tail ends. Because restenosis corresponds to the right tail end of the distribution curve, a discrepancy between mean neointimal volume and binary or clinical restenosis can occur in DES trials.[194,198,199] Similarly, bare metal stents show a wide individual variation in geographic distribution of neointima along the stented segment,[200] whereas some types of DES demonstrate predilection of in-stent neointimal hyperplasia for specific locations (e.g., proximal stent edge).[201] In serial IVUS studies with multiple long-term follow-ups, neointima within nonrestenotic bare metal stents showed mild regression after 6 months.[202] In contrast, both sirolimus- and paclitaxel-eluting stents showed a slight but continuous increase in neointimal hyperplasia for up to 4 years.[203-206]

Guidance of Procedures

In DES, the fact that the drugs dramatically reduce the variability of the biologic response (neointimal proliferation) further strengthens the prognostic value of the MSA as a powerful predictor for in-stent restenosis.[207-211] This was well illustrated in recent IVUS work by Sonoda and colleagues, in which sirolimus-eluting stents showed a stronger positive relation, with a greater correlation coefficient between baseline MSA and 8-month MLA, compared to control bare metal stents (0.8 versus 0.65 and 0.92 versus 0.59, respectively).[207] The utility of IVUS to ensure adequate stent expansion cannot be overemphasized, particularly if there are clinical risk factors for DES failure (e.g., diabetes, renal failure).

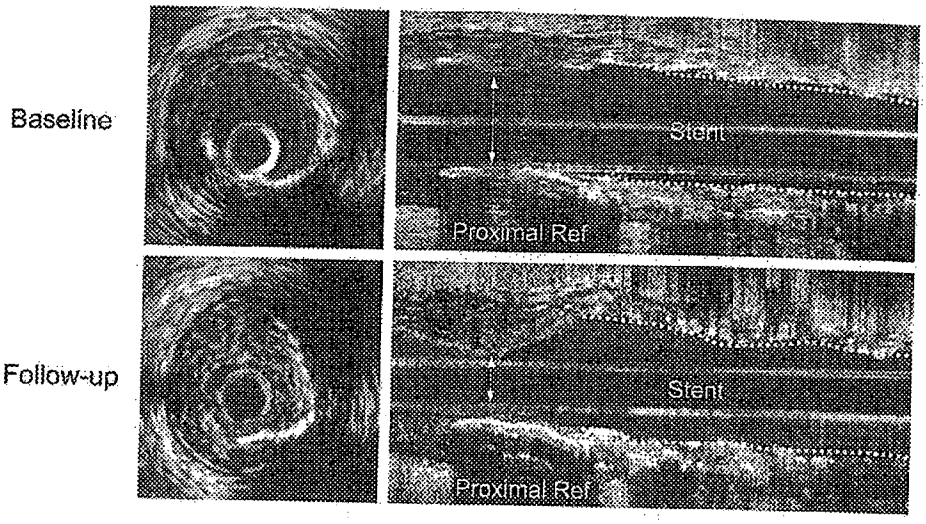

Figure 62-14. Proximal disease development 8 months after drug-eluting stent implantation. In this example, the new stenosis at the proximal stent margin is primarily caused by plaque proliferation, despite minimal neointimal hyperplasia observed inside the stent. Baseline intravascular ultrasound (IVUS) reveals a significant residual plaque at the corresponding uncovered segment.

In this context, preinterventional IVUS can also provide useful information about plaque composition. In particular, calcified plaque is important to identify, because the presence, degree, and location of calcium within the target vessel can substantially affect the delivery and subsequent deployment of coronary stents (see Fig. 62-5).[212,213] One important advantage of online IVUS guidance is the ability to assess the extent and distance from the lumen of calcium deposits within a plaque. For example, lesions with extensive superficial calcium may require rotational atherectomy before stenting.[213,214] Conversely, apparently significant calcification on fluoroscopy may subsequently be found by IVUS to be distributed in a deep portion of the vessel wall or to have a lower degree of calcification (calcium arc <180 degrees). In these cases, stand-alone stenting is usually adequate to achieve a lumen expansion large enough for a DES.

The discovery of "edge effects" associated with ICRT raised the concern of lumen narrowing in adjacent reference segments as a potential limitation of DES. However, current clinical experience with sirolimus- and paclitaxel-eluting stents has shown no accelerated edge restenosis overall, compared with conventional bare metal stents. A detailed serial IVUS analysis from the SCORE trial revealed that the favorable edge effect was primarily due to lack of vessel shrinkage, despite similar amounts of plaque proliferation, compared with the control group.[215] Similar vessel responses were reported in the Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT), TAXUS-II, and TAXUS-IV.[196,216,217] On the other hand, some DES trials demonstrated less effective suppression of late lumen loss at the proximal stent edge segment compared with the distal edge, possibly providing an important clue for optimal deployment of DES. In an IVUS substudy of the Sirolimus-Eluting Stent in De Novo Coronary Lesions (SIRIUS) trial, lesions with stent edge stenosis (>50% diameter stenosis) at 8 months had greater reference plaque burden (61% versus 49%; $P = .03$) (Fig. 62-14) and a higher overexpansion index (maximum stent area/reference MLA, 1.8 versus 1.5; $P = .03$) at baseline, compared to those without edge stenosis.[218]

More recently, the Stent Deployment Techniques on Clinical Outcomes of Patients Treated with the Cypher Stent (STLLR) trial also demonstrated that geographic miss (defined as the length of injured or stenotic segment not fully covered by DES) had a significant negative impact on both clinical efficacy (target vessel and lesion revascularization) and safety (myocardial infarction) at 1 year after sirolimus-eluting stent implantation.[219] These findings suggest that less aggressive stent dilation and complete coverage of reference disease may be beneficial, as long as significant underexpansion and incomplete strut apposition are avoided. On-line IVUS guidance can facilitate both the determination of appropriate stent size and length and the achievement of optimal procedural end points, with the goal being to cover significant pathology with reasonable stent expansion while anchoring the stent ends in relatively plaque-free vessel segments.

Insights into Long-Term Outcomes

Because of the low incidence of DES failure, clarification of its exact mechanisms awaits the cumulative analysis of large clinical studies. Nevertheless, suboptimal deployment or mechanical problems appear to contribute to the development of both restenosis and thrombosis. Particularly, the most common mechanism is stent underexpansion, the incidence of which has been reported as 60% to 80% in DES failures.[210,211,220] In a study of 670 native coronary lesions treated with sirolimus-eluting stents, the only independent predictors of angiographic restenosis were postprocedural final MSA and IVUS-measured stent length (OR = 0.586 and 1.029, respectively).[208] Recurrent restenosis after DES implantation for bare metal

stent restenosis was also recently investigated using IVUS. In a series of 48 in-stent restenosis lesions treated with sirolimus-eluting stents, 82% of recurrent lesions had an MSA of less than 5.0 mm², compared with only 26% of nonrecurrent lesions (P = .003).[220] In addition, a gap between sirolimus-eluting stents was identified in 27% of recurrent lesions versus 5% of nonrecurrent lesions. These observations emphasize the importance of procedural optimization at DES implantation for both de novo and in-stent restenosis lesions.

Although published data on DES thrombosis are further limited, one single-center IVUS study reported stent underexpansion (P = .03) and a significant residual reference segment stenosis (P = .02) as independent multivariate predictors of sirolimus-eluting stent thrombosis (median time, 14 days after implantation).[221] For very late DES thrombosis (>12 months), another investigator group also suggested smaller stent expansion and incomplete stent apposition as possible risk factors.[222]

Late-acquired incomplete stent apposition with DES has been reported in both experimental (paclitaxel)[223] and clinical (sirolimus and paclitaxel) studies (see Fig. 62-13).[193,196,224,225] Several IVUS studies indicated that the main mechanism is focal, positive vessel remodeling, as in the case of brachytherapy.[193,224] In addition, there is a strong suggestion that incompletely apposed struts are seen primarily in eccentric plaques, and that the gaps develop mainly on the disease-free side of the vessel wall. The combination of mechanical vessel injury during stent implantation and biologic vessel injury with pharmacologic agents or polymer in the setting of little underlying plaque may predispose the vessel wall to chronic, pathologic dilation. At present, however, no data directly link this finding with subsequent unfavorable clinical events such as late stent thrombosis.[226] Nevertheless, the potential impact of this finding on long-term outcomes needs to be carefully assessed over an extended period.

Other IVUS-detected conditions that may be of importance in DES include non-uniform stent strut distribution and strut fractures after implantation (Fig. 62-15).[227-230] Theoretically, both abnormalities can reduce the local drug dose delivered to the arterial wall, as well as mechanical scaffolding of the affected lesion segment. A recent IVUS study of 24 sirolimus-eluting stent restenoses identified the number of visualized struts (normalized for the number of stent cells) and the maximum interstrut angle as independent multivariate IVUS predictors of both neointimal hyperplasia and MLA.[228] In contrast, the exact incidence and clinical implications of strut fractures remain to be investigated.[231,232]

SAFETY

As with other interventional procedures, the possibility of spasm, dissection, and thrombosis exists when intravascular imaging catheters are used. In a retrospective study of 2207 patients, Hausmann and colleagues identified spasm in 2.9% of patients, and other complications, including dissection, thrombosis, and abrupt closure with "certain relation" to IVUS, in 0.4%.[233] This study was performed with first-generation catheters in the early 1990s, and it is likely (although not documented) that the incidence of spasm and other complications is substantially lower with the current generation of catheters.

COSTS

In the United States, current retail sales prices for the stand-alone single-use imaging catheters range between $600 and $850. The retail price of the IVUS imaging consoles is between $150,000 and $250,000, although the actual prices paid by hospitals vary widely depending on "bundling" deals and other special purchase arrangements. The U.S. Health Care Financing Administration approved reimbursement for the IVUS procedure and interpretation for Medicare patients in 1997, based on the number of vessels imaged. A number of other carriers have also approved reimbursement for IVUS, although payment is on a region-by-region basis. In most places, the total reimbursement is less than the cost of the catheters.

ONGOING AND ANTICIPATED TECHNICAL DEVELOPMENTS

Three-Dimensional Transducer Tracking

Compared with external imaging methods, one technical disadvantage common to catheter-based imaging modalities is difficulty in obtaining accurate spatial orientation of the investigated vessel segment. To overcome this limitation, three-dimensional transducer navigation or tracking techniques have been introduced by several investigator groups. In IVUS, this can be accomplished by reconstructing the three-dimensional pull back trajectory, using biplane x-ray recordings of the transducer,[234] or by real-time tracking of a miniaturized electromagnetic position sensor mounted in the catheter tip.[235] Computational algorithms and instrumentation have been developed to reduce significant artifacts induced by respiratory and cardiac motions.

The geometrically correct three-dimensional IVUS reconstruction of vessel wall structure may not only facilitate routine percutaneous interventions in complex coronary anatomy, but also allow detailed in vivo profiling of intracoronary hemodynamics and endothelial shear stress.[236,237] A number of pathologic and experimental studies have shown that inhomogeneities and irregularities of these factors play an important role in the initiation, localization, growth, composition, remodeling, and destabilization of atheromatous plaque.[238] A recent human in vivo study with the spatially correct three-dimensional IVUS partly confirmed these observations in a clinical setting, directly relating local endothelial

Circulation

American Heart Association
Fighting Heart Disease and Stroke

Volume 90, Number 5 November 1994

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73-0174(SP) ISSN 0009-7322

Circulation will be published twice each month beginning January 1995.

Do Fish Oils Prevent Restenosis After Coronary Angioplasty?

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Background The omega-3 polyunsaturated fatty acids derived from fish oils have been shown to modulate many factors believed to affect the pathogenesis of atherosclerosis. Because certain features of restenosis following angioplasty mimic some of the early changes of atherogenesis, some researchers have suggested that fish oil might prevent restenosis following angioplasty. We report the effects of omega-3 fatty acids on the rate of restenosis following percutaneous intraluminal coronary angioplasty (PTCA).

Methods and Results From August 1989 through September 1992, 551 patients were randomized to start receiving a daily dietary supplement of ten 1.0-g capsules containing 80.6% ethyl esters of omega-3 fatty acids providing 4.1 g eicosapentaenoic acid (EPA) and 2.8 g docosahexaenoic acid (DHA) for 6 months or an equal amount of an ethyl ester of corn oil. Four hundred seventy subjects who were well matched for risk factors completed successful angioplasty of one or multiple lesions in native coronary vessels and constituted the study cohort, of whom 447 were evaluable at 6 months after PTCA. The criteria for restenosis were that the quantitative coronary angiography at 6 months show a >30% increase in narrowing at the stenosis site or loss of at least half of the gain achieved at the time of PTCA and final restenosis with <50% luminal diameter remaining. In 93% of the patients, the end point was determined by angiography and in all except 1% of these by quantitative coronary angiography. Compliance with the fish oil supplement was good as judged by incorporation of EPA and DHA in plasma and red blood cell phospholipids. The restenosis rate among analyzable patients was 46% for corn oil and 52% for fish oil ($P=.37$). The addition of 200 mg α-tocopherol for all subjects during the study had no effect on restenosis rates.

Conclusions This was the largest of such trials to date, and a supplement of 8 g/d of omega-3 fatty acids failed to prevent the usual high rate of restenosis after PTCA. No adverse effects were attributable to this large daily supplement of omega-3 fatty acids. (*Circulation*. 1994;90:2248-2257.)

Key Words: • restenosis • angioplasty • fish oil • fatty acids

Several epidemiological studies[1-4] have suggested that there is an inverse relation between mortality from coronary heart disease and the dietary intake of omega-3 fatty acids derived from marine vertebrates. There also is considerable evidence that dietary fish oil supplements may reduce experimental atherosclerosis in some animals.[5-8] Laboratory studies have demonstrated that the ingestion of omega-3 fatty acids reduces the production in vivo of several factors believed to be atherogenic and increases the production of some antiatherogenic substances (reviewed in Reference 9).

Received March 29, 1994; revision accepted June 10, 1994.

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Because some features of the pathology, particularly the prompt proliferative response of arterial smooth muscle cells at the site of percutaneous transluminal coronary balloon angioplasty (PTCA), mimic features that characterize stages of atherosclerosis, it was suggested that ingestion of fish oils might prevent the high restenosis rate associated with angioplasty. Also, there appeared to be clear advantages to testing the effects of the fish oils on restenosis after PTCA: (1) The time necessary for such a study is relatively short since more than 80% of procedures that restenose will do so within 6 months of the procedure.[10] (2) The restenosis rate is high, ≈50% when quantitative coronary angiography (QCA) is done by 6 months,[11] despite present treatments. (3) Objective end points can be achieved with exit angiography. (4) There are more than 250 000 coronary angioplasty procedures performed annually in the United States,[12] so significant prevention of restenosis by fish oil would be highly cost effective for this expensive procedure.

There have been nine reported clinical restenosis studies with fish oil supplements.[13-21] These have achieved mixed results. One meta-analysis,[22] which analyzed data from the first seven studies, concluded that although the combined data were "compatible with a small to moderate benefit of fish oil on restenosis, these results require confirmation in a randomized clinical trial large enough to distinguish reliably between a

clinically meaningful benefit and a null result.[17] The numbers of subjects in individual studies were too small, the procedures varied considerably among the studies, the dose and form of omega-3 supplement varied as did the time of supplement commencement in relation to PTCA, and end points for restenosis were not always rigorous. A second meta-analysis reported the following year was less critical of the evidence.[23]

We report the results of a prospective, randomized, placebo-controlled, double-blind clinical trial designed to test the hypothesis that a dietary supplement of fish oil, given daily from 12 to 14 days before through 6 months after angioplasty, will reduce the frequency of restenosis.

Methods

From August 1989 through September 1992, 551 patients were randomized to start receiving a daily dietary supplement of 10 1-g gelatin capsules containing 80.6% ethyl esters of omega-3 fatty acids providing 4.1 g eicosapentaenoic acid (EPA) and 2.8 g docosahexaenoic acid (DHA) with 12 mg α-tocopherol and 28 mg γ-tocopherol or an equal amount of an ethyl ester of corn oil as placebo (provided by the Biomedical Test Materials of the National Institutes of Health and produced by the National Marine Fisheries Service Laboratory). The corn oil and fish oil capsules were dispensed by the research pharmacist at each collaborating center according to a randomization schedule generated by the study statistician. At each center, only the research pharmacist was unblinded to the treatments. At the Data Coordinating Center, only the statistician and principal investigator were unblinded. To blind the patients to capsule contents, a very small amount (0.4%) of fish oil was added to the corn oil, yielding 2 and 1.2 mg/d of EPA and DHA, respectively. To check the accuracy of dispensed capsules, capsules were sent periodically from each center by the research pharmacist to the principal investigator for analysis of contents. All analyses confirmed correct assignment in accord with the randomization schedule.

All patients received instructions on following a Step-One American Heart Association diet[24] for the duration of the study, and this was reinforced during monthly telephone interviews with each patient throughout the study. However, examination of individual patients' questionnaire responses indicates that there was considerable variation in compliance. Patients were recruited at eight separate collaborating centers, but three of these each contributed 20% to 25% of the enrollees. Patients were treated with other medications prescribed by their physician, but all patients received 325 mg/d aspirin throughout the 6 months of the study. The protocol for this clinical trial is presented in Fig 1 and indicates the sequence of studies performed during the clinical trial.

Inclusion Criteria

Patients who were evaluated and scheduled for elective PTCA of one or multiple lesions in native coronary arteries and were willing to participate were candidates for inclusion in the study. Only patients with lesions in native vessels that caused ischemic symptoms or who had ≥50% stenosis as determined by QCA and had not undergone prior angioplasty were eligible.

Exclusion Criteria

Exclusion criteria were questionable compliance; receiving steroid therapy or immunosuppressive drugs; associated nonatherosclerotic heart disease; aspirin intolerance; serious illness other than stenosis with expected survival of <2 years; stroke within 6 months; poorly controlled, sustained hypertension; pregnancy; age >80 years; <12 days remaining between enrollment and scheduled PTCA, preventing 12 days of oil

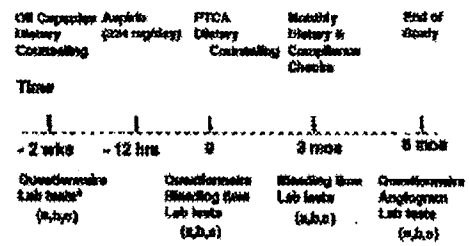

FIG 1. Diagramatic of study design and intervention schedule. The letters following the designation "laboratory studies" indicate routine hematocrit, hemoglobin, white blood cell count, and platelet count (a); plasma lipid profile (total, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides) (b); and phospholipid fatty acids in plasma and in red blood cells (c). Urine samples were collected for urinary eicosanoids at entry, percutaneous transluminal coronary angioplasty (PTCA), and exit.

supplementation before PTCA; diffuse lesions (>2 cm long), excessive tortuosity of proximal segment, or extremely angulated segments (>90°); previous PTCA/coronary artery bypass graft surgery (CABG) to vessel; and <6 months since previous PTCA or myocardial infarction.

Definition of Successful Angioplasty

The criterion for successful angioplasty is a ≥10% reduction in stenosis by QCA or 20% by visual analysis, leaving a residual stenosis of <50%. Patients subjected to PTCA have several possible initial outcomes: (1) a successful procedure; (2) technical failure to adequately relieve the stenosis, as inability to insert the balloon catheter into the stenotic segment; and (3) acute closure of the PTCA site that cannot be redilated while the patient is still in the catheterization laboratory. To be included in the study, outcome 1 must occur. Because the purpose of the study was to determine the ability of fish oils to prevent restenosis, this can be judged only if a satisfactory PTCA is obtained initially.

Definition of Restenosis

The criteria for restenosis are that QCA of the angiogram by 6 months shows >30% increase in narrowing at the stenosis site or loss of at least half of the gain achieved at the time of successful PTCA and a final restenosis with <50% luminal diameter remaining.[25]

PTCA Procedure

PTCA was performed using an over-the-wire system. On the day before the procedure, patients started receiving a calcium channel blocker (60 to 90 mg diltiazem TID or 10 to 20 mg nifedipine TID) and 325 mg/d aspirin. Patients in the fasting state were pretreated with diazepam and diphenylhydramine. Heparin (10 000 U IV) was administered, followed by 5000 U IV every hour during the angioplasty. Before dilation of the coronary artery, 200 μg nitroglycerin was administered, and coronary cineangiograms of the obstructed vessels were obtained using standard projections similar to those used in the National Heart, Lung, and Blood Institute TIMI trial.[26] The angioplasty was complete when there was angiographic evidence of >20% reduction in stenosis with a hemodynamically insignificant residual stenosis (<50%). The angioplasty equipment was then withdrawn, and 200 μg nitroglycerin IC was administered.

After the procedure, the arterial and venous sheaths were removed 4 hours after the last bolus of heparin. Alternatively, arterial and venous sheaths were left in place, and systemic heparin was continued as clinically indicated. On discharge, patients were maintained on aspirin, oil capsules, diet, and other indicated therapy for the following 6 months.

Each cardiac catheterization facility was standardized for uniformity of procedure. Quantitative measurements were calibrated using the guiding catheter as the reference dimension. This allowed absolute dimensions of all vessel diameters to be quantified and compared. In addition to the standard projections, the best camera angles for visualization of stenotic areas were filmed together with paired orthogonal views, and the angles were recorded for reproducible positioning on subsequent filming. The locations in the coronary arteries of the index lesion that underwent angioplasty in this study were left anterior descending, 26%; left circumflex, 10%; right coronary, 29%; other, 10%; and multiple vessels, 26%, with no differences between the corn oil and fish oil groups.

Repeat angiography was performed during the 6 months of follow-up for recurrence of ischemic symptoms and in all patients at 6 months. If a repeat angiogram was indicated at 4 months or later, no repeat angiogram was requested at 6 months. Before the repeat angiogram, 200 μg nitroglycerin IC was administered, and cineangiograms were obtained of the dilated sites using the same camera projections as on the prior angiograms.

Angiograms were interpreted quantitatively (CAAS) at the completion of the study at a single site (Baylor) by the same interpreter (A. Raizner, MD), from whom the sequence of the films was withheld as well as knowledge of which oil supplement the patient had received. Ten percent of films (films of 45 of 463 patients, including rereading of 62 of 615 lesions) were returned, under a different code number for repeat reading to determine the reproducibility of the quantitative interpretations. The pooled coefficient of variation for the paired readings was 11.5% for percent diameter stenosis.

Laboratory Procedures

Plasma lipid levels (total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides) were determined at one Centers for Disease Control and Prevention–certified laboratory (Medical Research Laboratory, Inc, Cincinnati, Ohio), and low-density lipoprotein (LDL) cholesterol level was calculated with the Friedwald equation.[27] Lipoprotein (a) [Lp(a)] was determined at the laboratory of Dr E.J. Schaeffer (Tufts New England Medical Center). The fatty acids of phospholipids of serum and red blood cell ghosts were extracted by the method of Bligh and Dyer,[28] and the phospholipids were separated from other lipid fractions by thin-layer silicic acid chromatography, hydrolyzed, and analyzed after methylation by gas chromatography in the Core Laboratory of the General Clinical Research Center at the Massachusetts General Hospital. Bleeding time determinations were performed by a trained technician at each collaborating center using the automated Surgicutt method. Routine blood counts were performed by the clinical laboratory at each center.

The excretion of urinary eicosanoid metabolites was measured as described in detail previously.[29,30] In brief, thromboxane excretion was analyzed by radioimmunoassay using a thromboxane antibody that cross-reacts with metabolites of dienoic and trienoic thromboxanes, thromboxane (TX)$B_{2/3}$ and 2,3-dinor-$TXB_{1/3}$. Excretion of 2,3-dinor-6-keto-prostaglandin (PG)$F_{1\alpha}$ (PGI_2-M) and Δ17-2,3-dinor-6-keto-$PGF_{1\alpha}$ (PGI_3-M), the major urinary metabolites of PGI_2 and PGI_3, respectively, which are derived form arachidonic acid and EPA, respectively, was analyzed with a stable isotope dilution assay by negative ion–chemical ionization gas chromatography–mass spectrometry. After extraction of 30 to 50 mL of urine, we prepared pentafluorobenzyl ester-methoxime-1 trymethylsilyl ether derivatives, and fragments m/z 586 and 584 of the endogenous PGI_2-M and PGI_3-M, respectively, were monitored as well as fragment m/z 589 of the trideuterated standard (4 mg) added before extraction.

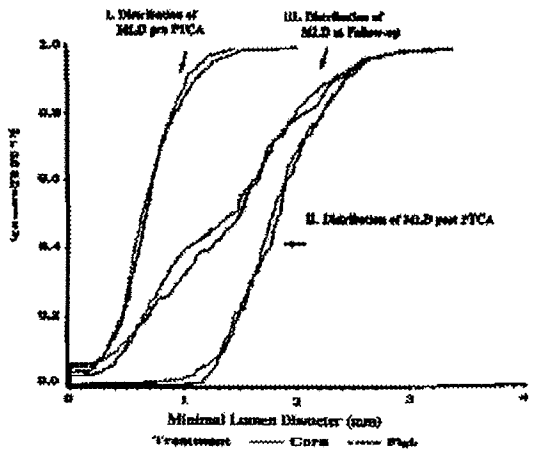

Fig 2. The cumulative distribution probability curve of the minimal lumen diameter (MLD) (ie, lumen diameter [mm] at the maximally stenotic site) before percutaneous transluminal coronary angioplasty (PTCA), after PTCA, and at exit follow-up in both treatment groups by lesion. It can be seen that initial degree of stenosis before PTCA and amount of dilatation achieved at angiography were very comparable between the two treatment groups.

Statistical Analysis

The independence of lesions in the same patient was determined using a χ^2 test to test the null hypothesis that among patients with two lesions, the number of patients with none, one, or two restenoses would be $(1-p)^2$, $2p(1-p)$, and p^2, respectively, with p being the restenosis rate—in this case, 0.41. There were 79 patients who had two index lesions in this study, and 41% of these 158 lesions had restenosis. If restenosis in the two lesions was independent, then we would expect 48% of the patients to have restenosis in one lesion, 17% to have restenosis in two lesions, and 35% to not have any restenosis. Instead, 25% of patients had restenosis in two lesions and 43% had no restenosis. This was significantly different than would be expected with independence of the lesions to restenose ($P<.005$). Analysis of restenosis rates, therefore, was made per patient, not per lesion, in those subjected to PTCA of multiple vessels (ie, if one or both index lesions restenosed, the patient was counted as a "restenosis"), except for the data presented in Figs 2 and 3. There were no significant differences in the anatomic locations of the index lesions by treatment (corn oil compared with fish oil groups), including lesions in the left anterior descending coronary artery, 27% versus 25%; left circumflex artery, 12% versus 8%; right coronary artery, 29% versus 28%; multiple coronary vessels, 23% versus 28%; and other sites, 9% versus 11%, respectively.

For analyses in which the value of n was <50% in each treatment group of the total 447 analyzable patients, difficulty in collection of samples or their preservation, not nonrandom selection of samples, was the problem.

A treatment effect on restenosis was determined by a χ^2 test. No adjustment was made for multiple comparisons in testing for treatment effects within subgroups. Quantitative data were analyzed using parametric statistics, ie, t tests and Pearson correlation coefficients.

Results

Patient Characteristics

Table 1 shows pertinent patient demographics by treatment group and the eligibility of a patient for inclusion in the study based on the initial QCA entrance

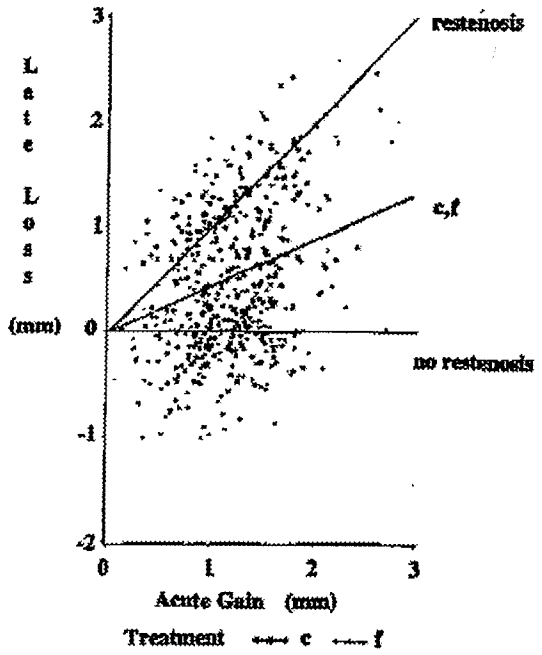

FIG 3. Plot of relation of "Late Loss" (restenosis) to "Acute Gain" (from percutaneous transluminal coronary angioplasty [PTCA]) per lesion. The horizontal line represents no restenosis. The line of identity represents restenosis, ie, total loss of gain in minimal lumen diameter (MLD). The lines representing the least-mean-squares curves of the fish oil (f) and corn oil (c) groups are essentially superimposable and lie approximately between these limiting parameters, consistent with the approximately 50% restenosis that occurred in both treatment groups. There were 45 corn oil and 48 fish oil lesions represented above the line of identity, indicating a restenosis in excess of the gain in MLD at PTCA. By contrast, 77 corn oil and 72 fish oil lesions showed further regression after PTCA. They are represented by the symbols that fall below the line of no restenosis. The remainder of 125 corn oil and 150 fish oil lesions are represented by symbols falling between the line of identity and the horizontal line.

TABLE 1. Patient Demographics at Entry

	Treatment	
	Corn Oil (n=221)	Fish Oil (n=226)
Age, %		
30-39 y	4	4
40-49 y	20	19
50-59 y	37	27
60-69 y	38	38
≥70 y	11	12
Sex, % male	81	77
Eligible by QCA, %	97	99
Successful by QCA, %	97	98
Diabetic, %	18	14
History of hypertension, %	37	47
Diastolic BP, mm Hg	76.7±0.7	76.9±0.6
Systolic BP, mm Hg	129.9±1.2	130.8±1.1
History of smoking, %	76	77
Currently smoking, %	19	14
History of MI, %	33	33
Years of CAD	2.1	2.2
History of angina, %	68	68
CCS class*, %		
I	14	17
II	36	42
III	29	25
IV	6	3
Previous PTCA, %	4	7
Previous CABG, %	3	5

QCA indicates quantitative coronary angiograph; BP, blood pressure; MI, myocardial infarction; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society classification of the severity of angina; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass graft surgery. Only for the history of hypertension was a significant difference ($P=.04$) present between the two treatment groups. The high percentages for eligibility by QCA indicate the very good agreement between retrospective QCA interpretations at a single core laboratory site and the visual interpretations made initially at each collaborating center.

criteria; the only significant difference was for a history of hypertension ($P=.04$). There were no significant differences by treatment of the major types of lesions that were treated. In 116 patients (26%), the angioplasty procedure included more than one vessel. Because a clear indication was found that patients who had restenosis in one lesion had a greater chance of restenosis in another lesion, the analysis of restenosis rates was made per patient, not per lesion, in those subjected to PTCA of multiple lesions.

Patient Follow-up

Table 2 is a flow chart indicating patient status at several times during the study. Of the 551 patients initially randomized into the study, 71 enrollees were disqualified, most because of late medical decisions that PTCA was not the proper management for them; a few were unable or unwilling to take the corn or fish oil capsules. Four-hundred-seventy patients had a satisfactory PTCA, of whom 447 were evaluable, for a 4.9% attrition rate following PTCA. Of the 447 evaluable patients, 409 had QCA analyses of their three angiograms. In 7 other patients, the exit angiograms were interpreted visually rather than by QCA, because the exit angiograms were unavailable for the quantitative interpretation. Three patients directly underwent CABG without intervening angiography, and there was one sudden death. Thus, 93% of evaluable patients were judged on the basis of angiographic findings, and all except 1% of these were by QCA. The remaining 27 evaluable patients were evaluated by two cardiologists blinded to treatments who based their judgments on clinical finding, such as recurrence or worsening of angina or occurrence of nonfatal myocardial infarction, or on laboratory results, such as ECG or exercise stress tests with thallium scintography.

TABLE 2. Status of Patients Throughout the Study

Study Stages	Corn Oil	Fish Oil	Total
Patients randomized	276	275	551
Disqualified before PTCA	26	22	48
PTCA performed	250	253	503
Unsuccessful PTCA	18	15	33
Successful PTCA	232	238	470
Followed ≥3 months	219	218	437
Followed for 6 months	207	206	413
Unevaluable dropouts	11	12	23
Evaluable patients	221	226	447
Restenosis	101	117	218
No restenosis	120	109	229

PTCA indicates percutaneous transluminal coronary angioplasty.
Patients disqualified before PTCA include mainly patients whose preangioplasty angiogram or clinical course indicated that management other than by angioplasty was indicated. A few found the capsules too difficult or too stressful to tolerate. An unsuccessful PTCA occurred in 6.5% of patients. A total dropout of 12% of those who had a successful PTCA occurred, but only 4.6% were ultimately unevaluable. "Unevaluable" indicates that neither clinical nor laboratory evidence was available to judge final designation of restenosis. In the 116 patients who had angioplasty for more than one vessel, a restenosis in one or more of the treated vessels included that patient in the restenosis group.

Restenosis Rates

The restenosis rate among analyzable patients was 46% for corn oil recipients and 52% for fish oil recipients ($P=.37$). Fig 2 shows the distribution function of the minimal lumen diameter (MLD) at the site of PTCA before and immediately after PTCA and at the 6-month follow-up angiogram for the two treatment groups; the curve represents the proportion of lesions that had a MLD less than the value on the abscissa. The correlation coefficient was .17 ($P<.0001$) for the severity of the initial stenosis and the probability of restenosis. Fig 3 is a plot of the late loss of MLD against the early gain in lumen diameter resulting from the angioplasty procedure for all lesions in the fish and corn oil groups. Complete restenosis would have fallen on the line of identity with a slope of 1.0, and no restenosis would be depicted by a horizontal line. Although there is much scatter of the data, clearly the preponderance of results indicates some restenosis, and no difference is seen between the line of best fit for the fish oil and corn oil treatment groups.

Because of concern that the supplement of polyunsaturated fatty acids in both corn and fish oil might increase damage to cells from lipid peroxidation, all patients were started on a daily supplement of 200 mg *dl*-α-tocopheryl acetate (Schein Pharmaceutical, Inc) in March 1991, when one third of the final number of patients had been enrolled. The addition of this dose of vitamin E did not affect the restenosis rates. For the 134 patients who received no vitamin E supplement, equally divided between the treatment groups, stenosis rates were 44% and 51% for the corn oil and fish oil groups, respectively. Of the 278 who received vitamin E throughout the study, rates were 47% and 54% for the corn oil and fish oil groups, respectively.

There were no significant differences between the two treatment groups for any of the patient characteristics listed in Table 1, except for history of hypertension. There were significant differences in restenosis rates for age, diastolic blood pressure with age, and Canadian Cardiovascular Society classification of angina (although class IV, with few patients, did not fit this relation). Paradoxically, patients who had a history of smoking or were currently smoking had significantly lower restenosis rates than did the nonsmokers ($P=.0063$ and .0008, respectively).

No significant differences occurred in the frequency of cardiac events (worsening of angina, angina on exit from study, myocardial infarction, congestive failure, CABG) by treatment groups. Two cardiac deaths occurred, both in the corn oil group. One patient had an unsuccessful PTCA leading to an emergency CABG, which the patient did not survive. The other death was sudden, occurring 3.5 months after PTCA. Because the first patient did not have a successful PTCA, he was not an evaluable subject. The second patient was judged to have a restenosis, although we lack postmortem documentation that it was the index lesion that led to the terminal event. No noncardiac deaths occurred.

Of the 218 patients who restenosed during the study according to the criteria used, 31% reported no angina and 65% experienced angina; of the 229 patients without restenosis, 65% had no angina and 24% did. Thus, one third of the restenoses occurred without angina, and slightly more than one fourth of patients without identified angiographic stenosis experienced angina. The relation between restenosis and angina or angina worsening was significant ($P<.001$ and .031, respectively).

Adverse Events

There were few adverse events by type and timing of their occurrence that resulted in either hospitalization or withdrawal from the study. This includes all patients rather than just those who completed treatment. There were 276 patients randomized to receive corn oil and 275 randomized to receive fish oil. No significant differences occurred between the treatment groups for any of the adverse events. There were 3% bleeding episodes and 4% infections noted in each treatment group. Gastrointestinal symptoms were reported in 8% of the corn oil recipients and 7% of the fish oil recipients; 3% of the corn oil recipients and 1% of the fish oil recipients withdrew from the study because of adverse cardiovascular events. There were no other miscellaneous adverse events affecting the study, and at no time during the course of the study did significant differences in events occur between treatment groups.

Laboratory Analyses

Table 3 gives the values for the standard plasma lipids, Lp(a), body weight, blood pressure, pulse, hemoglobin, hematocrit, white blood cell count, platelets, and bleeding time. Table 4 gives the concentrations of the pertinent fatty acids in the plasma phospholipids as a percentage of total fatty acids, with white blood cell and platelet counts. The values at entry were very similar for the treatment groups. Notable are the large expected

TABLE 3. Laboratory Findings Comparing the Two Treatment Groups at Entry, at Angioplasty, at 3 Months, and at Exit From the Study

	Entry		PTCA		3 Mo		Exit	
Treatment	Mean±SEM	n	Mean±SEM	n	Mean±SEM	n	Mean±SEM	n
Corn oil								
Weight, lb	184.9±2.0	275	...	0	185.1±2.2	209	184.9±2.3	197
Pulse	66.5±0.6	275	...	0	...	0	66.1±0.7	205
DBP, mm Hg	76.7±0.7	275	...	0	...	0	77.1±0.7	205
SBP, mm Hg	129.9±1.2	275	...	0	...	0	133.6±1.3	205
T-Chol	220.5±2.8	261	206.8±2.5	247	221.9±3.0	187	209.6±2.9	195
HDL-Chol	39.9±0.7	258	38.3±0.7	246	41.8±0.8	184	40.5±0.7	194
LDL-Chol	141.9±2.5	244	133.1±2.3	236	141.2±2.7	170	135.0±2.4	186
Triglycerides	207.2±8.6	259	179.9±7.5	246	217.7±17.4	186	180.0±11.7	195
Lp(a)	22.5±2.8	35	22.5±3.2	35	22.5±3.7	33	23.9±3.4	33
Hemoglobin	14.5±0.1	271	14.2±0.1	249	14.7±0.1	181	14.5±0.1	201
Hematocrit	42.9±0.2	271	41.7±0.2	249	43.4±0.3	181	42.4±0.3	201
WBC	7397±134	272	7530±125	249	7029±147	181	7100±136	201
Platelets	254.8±3.9	271	252.6±3.9	248	256.8±4.7	181	247.6±4.2	199
Bleeding time, min			6.34±0.2	225	6.47±0.2	171	...	...
Fish oil								
Weight, lb	179.0±1.9	274	...	0	178.2±2.2	205	176.0±2.2	197
Pulse	66.4±0.6	273	...	0	...	0	66.6±0.9	201
DBP, mm Hg	76.9±0.6	273	...	0	...	0	77.0±0.8	201
SBP, mm Hg	130.8±1.1	273	...	0	...	0	132.9±1.3	201
T-Chol	220.0±2.6	263	201.7±2.7	250	212.9±2.8	180	201.4±2.9	186
HDL-Chol	38.7±0.7	258	37.3±0.7	248	42.1±1.0	180	38.1±0.8	186
LDL-Chol	141.2±2.3	240	139.0±2.5	246	144.2±2.6	177	137.5±2.5	183
Lp(a)	23.3±3.5	32	24.9±3.4	32	20.2±2.9	27	22.0±3.5	29
Triglycerides	211.9±7.7	262	128.9±5.3	250	131.6±5.9	180	125.4±6.3	186
Hemoglobin	14.5±0.1	271	14.6±0.3	249	14.7±0.1	178	15.1±0.7	191
Hematocrit	42.7±0.2	270	41.3±0.3	250	43.3±0.3	178	42.5±0.3	190
WBC	7495±136	271	7430±135	249	6867±139	178	7047±163	190
Platelets	269.3±4.2	267	255.5±4.8	247	254.5±5.3	176	244.4±5.1	190
Bleeding time, min			6.22±0.2	222	7.02±0.2	170	...	...

PTCA, percutaneous transluminal coronary artery; DBP, diastolic blood pressure; SBP, systolic blood pressure; T-Chol, total cholesterol; HDL-Chol, high-density lipoprotein cholesterol; LDL-Chol, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); and WBC, white blood cells.

reduction in triglycerides by 41% in the fish oil group compared with 14% in the corn oil group and the reduction in total cholesterol in the fish oil group. Also of importance to this study is the evidence that with the fish oil supplement, EPA and DHA displaced arachidonic and linoleic acids in both plasma and red blood cell phospholipids (Fig 4A and 4B). Data are shown at entry (baseline), at PTCA, at 3 months, and on exit from the study (generally 6 months but earlier in ≈30% of patients whose recurrence of angina led to an early exit from the study).

There were no significant differences between the combined urinary metabolites of the dienoic and trienoic thromboxanes in the restenosis or no-restenosis patients in either the corn oil or fish oil group (data not shown). Because all patients were prescribed 325 mg/d aspirin, this is not a surprising finding. However, 41% and 48% of patients receiving corn and fish oil, respectively, had exit levels of thromboxane urinary metabolites of >50 ng/g creatinine, suggesting poor compliance with the daily aspirin prescription. When restenosis was examined as a function of aspirin compliance, however, no significant correlations were found. Urinary PGI_2 metabolite levels at exit were negatively correlated, as expected, with both EPA and DHA levels in the plasma and red blood cell phospholipids (for the red blood cells, $r=-.32$, $P=.004$; and $r=-.27$, $P=.02$ for EPA and DHA, respectively). With PGI_2, the correlations with plasma phospholipid levels were positive, also as expected ($r=.18$, $P=.05$; and $r=.23$, $P=.01$ for EPA and

TABLE 4. Pertinent Fatty Acids of Phospholipids of Plasma and of Red Blood Cells at Entry, at Angioplasty, at 3 Months, and at Exit From the Study

		Entry		PTCA		3 Mo		Exit	
Treatment	FA	Mean±SEM	n	Mean±SEM	n	Mean±SEM	n	Mean±SEM	n
Corn oil; plasma phospholipid fatty acids	Oleic	9.8±0.10	206	9.3±0.09	210	9.2±0.09	166	9.2±0.09	182
	LA	21.0±0.23	206	22.0±0.21	210	22.8±0.26	166	22.4±0.25	182
	AA	10.7±0.18	206	10.7±0.18	210	10.9±0.20	166	11.3±0.20	182
	LNA	0.13±0.03	206	0.11±0.02	210	0.10±0.02	166	0.10±0.02	182
	EPA	0.71±0.03	165	0.71±0.04	165	0.64±0.03	166	0.75±0.06	171
	DHA	2.71±0.09	203	2.73±0.09	205	2.79±0.10	166	2.96±0.11	180
Fish oil; plasma phospholipid fatty acids	Oleic	9.7±0.10	202	8.6±0.09	206	8.5±0.11	167	8.5±0.09	176
	LA	20.4±0.22	204	16.2±0.21	207	17.2±0.26	167	17.8±0.24	179
	AA	10.9±0.17	204	9.0±0.14	207	7.6±0.15	167	7.9±0.15	179
	LNA	0.09±0.02	204	0.05±0.01	207	0.10±0.02	167	0.10±0.02	179
	EPA	0.83±0.06	192	5.6±0.14	206	6.2±0.19	167	6.0±0.21	178
	DHA	2.9±0.09	202	5.4±0.15	201	5.8±0.19	167	6.2±0.17	176
Corn oil; RBC phospholipid fatty acids	Oleic	14.8±0.26	87	14.4±0.23	93	14.0±0.18	88	13.9±0.22	95
	LA	10.8±0.20	87	11.0±0.21	93	11.4±0.18	88	11.2±0.21	95
	AA	15.3±0.42	87	15.3±0.43	93	15.8±0.34	88	15.8±0.36	95
	LNA	0.08±0.03	87	0.04±0.02	93	0.07±0.03	86	0.03±0.02	93
	EPA	0.5±0.04	87	0.5±0.04	93	0.6±0.04	88	0.7±0.07	94
	DHA	4.1±0.14	87	4.1±0.17	93	4.4±0.14	88	4.5±0.17	95
Fish oil; RBC phospholipids fatty acids	Oleic	14.9±0.27	83	14.2±0.23	85	14.1±0.20	84	13.8±0.19	95
	LA	10.8±0.17	83	9.1±0.15	85	9.0±0.19	84	9.0±0.19	95
	AA	15.7±0.41	83	15.1±0.40	85	11.6±0.28	84	11.2±0.30	95
	LNA	0.06±0.03	83	0.10±0.05	84	0.13±0.05	82	0.06±0.03	89
	EPA	0.5±0.05	83	2.42±0.11	85	4.6±0.20	84	4.9±0.20	95
	DHA	4.1±0.16	83	5.0±0.17	85	7.8±0.21	84	8.3±0.19	95

FA indicates fatty acid; PTCA, percutaneous transluminal coronary angioplasty; LA, linoleic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; and DHA, docosahexaenoic acid; and RBC, red blood cells.

DHA, respectively). PGI_2 levels at exit in either treatment group were not significantly different for restenosis and no-restenosis patients. However, with PGI_2, for corn oil–supplemented patients (n=29) who restenosed, the mean level of urinary metabolites was 0.17±0.09 ng/g creatinine at exit, whereas the value for patients with no restenosis (n=48) was 1.02±0.24 ng/g creatinine (P=.002). This finding is unexplained as in the fish oil–supplemented patients who restenosed, PGI_2 excretion values were 10-fold higher.

Discussion

The present study was a randomized, double-blind, placebo-controlled clinical trial that included 474 evaluable patients who had undergone successful angioplasty 6 months earlier. The number of patients was calculated with the following assumptions: the expected rate of restenosis at 6 months after PTCA was 30%; a 33% reduction in the restenosis rate from our intervention would be considered a therapeutic success; α error was .05; and power was .80. The calculation indicated a need for 230 patients in the placebo group receiving corn oil containing polyunsaturated omega-6 fatty acids and in the intervention group receiving a concentrated fish oil preparation containing omega-3 polyunsaturated fatty acids. With the definition of restenosis used as the primary end point of this study, the observed restenosis rate judged by QCA was ≈50%, which is consistent with what has been reported when similar criteria of restenosis were used and QCA interpretation was applied to all study subjects.[11] This higher-than-expected restenosis rate should have made it easier to detect a significant effect of the fish oil intervention on reducing the restenosis rate had such an effect existed. Furthermore, the high restenosis rate in each group indicates that the failure to detect an effect of the fish oil supplement was not due to a beneficial effect that was masked by a similar beneficial effect from the corn oil supplement. The 95% confidence interval for the decrease in the risk of restenosis with fish oil compared with corn oil was −37% to +6%. Thus, the data were consistent with, at

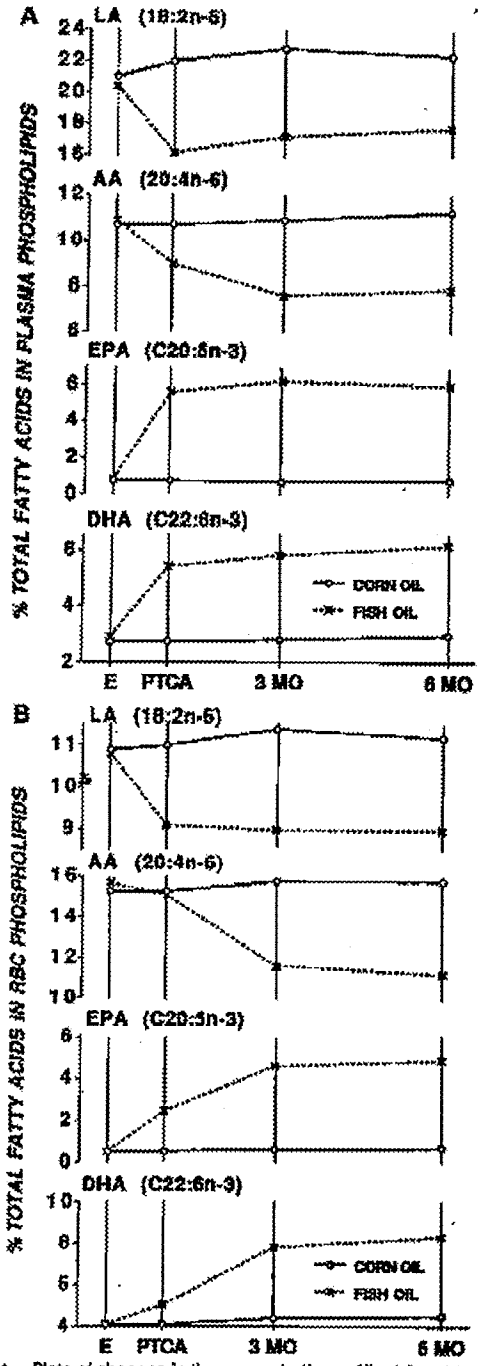

FIG 4. Plots of changes in the concentrations of linoleic acid (LA), arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are shown expressed as percent of fatty acids in plasma (A) and red blood cell (B) membrane phospholipids comparing the corn oil– with the fish oil–supplemented patients. Levels of these fatty acids attained a steady state in plasma phospholipids by the time of percutaneous transluminal coronary angioplasty (PTCA). However, in red blood cell membrane phospholipids, steady-state levels were apparent only by 3 months. The maintenance of steady-state levels until exit from the study indicates good compliance of subjects with ingestion of supplements.

most, a 6% reduction in risk due to fish oil, a reduction judged not to be clinically significant.

There have been nine previous reports of restenosis trials with fish oil, and they have had mixed results.[13-21] One meta-analysis[22] of seven of these trials concluded that a small beneficial effect existed but that confirmation was needed in a randomized trial large enough "to distinguish reliably between a clinically meaningful benefit and a null result." The size of the present study was calculated to show a significant difference, if one existed. When the results of the present study are included in this meta-analysis (even without inclusion of two other recent studies,[20,23] both of which were negative), the overall result is no longer statistically significant. It is notable, however, that the original meta-analysis[22] noted a significant heterogeneity between the studies that becomes even more significant ($P=.004$) when the present study is included. This could indicate that some factor, involving either treatment or patient population, that was present in some studies and not in others may be responsible for differences in the effect of the fish oil treatment.

There are a number of differences in design other than size of the individual studies that deserve comment. The end point selected may change the total percentage of restenoses diagnosed, but because the same criteria apply to both control and intervention cohorts, it would not hide a significant difference. In addition to the definition of restenosis used in this study, one can see from Fig 3 that when all the angiographic data for each patient are plotted as "acute change" (the difference between lumen diameter at the stenotic site just before and that just after angioplasty) against the "late loss" (the difference in lumen diameter at exit and that on post-PTCA angiograms), there is no significance difference in the lines of best fit for the corn oil group versus the fish oil group.

The time before PTCA when the oil supplements were started was another variable among published studies. Since the stimulus for repair at the site of angioplasty must be at or near maximal at the time of dilation of the stenotic site, it would seem essential that any protective measure be in place at the time of angioplasty. In some reported studies, the fish oil supplement was started on the day of the angioplasty or the next day, whereas in the Quebec study,[19] which showed a benefit, the oil supplement was started 3 weeks before angioplasty. We advised 14 days but compromised to make 12 days the minimal allowable interval before PTCA.

We chose to apply the very large dose of 8 g/d omega-3 fatty acids for the 6 months of the study. This supplement provided 4.1 g DHA (C22:6n-3) and 2.8 g EPA (C20:5n-3), the two highly unsaturated fatty acids to which antiatherogenic effects of fish and fish oil have generally been ascribed. This high dose, approaching the intake of Greenland Inuits, was chosen with the hope of overcoming any antagonistic effects of other fatty acids competing with those of EPA or DHA, such as arachidonic acid or saturated fats. Although all patients were prescribed a diet with 30% energy from fat, this study was intended as a test of the effects of a supplement not requiring strict additional dietary restrictions. This dose is higher than that used in any of the earlier studies, and it was administered as the ethyl

esters of the omega-3 fatty acids, which are well absorbed.[31] However, a recent report indicates that a high saturated fatty acid intake can diminish the potential benefits of a given intake of omega-3 fatty acids.[32]

With the high dose of supplements used, the plasma phospholipid levels of the omega-3 EPA and DHA rose promptly in association with a reciprocal decrease in omega-6 linoleic acid and arachidonic acid, so that at the time of PTCA steady-state levels were essentially achieved (Fig 4A). Such a prompt attainment of steady-state levels, however, was not achieved in the phospholipids of the red blood cells (Fig 4B). At the time of PTCA, EPA and DHA had achieved only 43% and 25%, respectively, of their subsequent steady-state increases, and arachidonic acid had hardly declined. Only the linoleic acid levels in the red blood cell phospholipids had reached their steady level. This raises a question of whether the period of pretreatment with the supplements before PTCA was adequate to attain optimal conditions to prevent restenosis. What we cannot know is what levels had been attained in the vessel wall at the site of angioplasty where the smooth muscle proliferation and other changes occur or whether any level of incorporation could have prevented the restenosis. The ample steady-state levels of EPA and DHA in the red blood cell phospholipids at 3 months and at exit support good compliance by our subjects to the supplements.

The blood lipid profile showed the characteristic large decrease in triglycerides in the group receiving fish oil (41% in this trial) but no other significant differences. With fish oil, both total and LDL cholesterol decreased minimally, and HDL cholesterol rose slightly but without reaching significance between the treatment groups. A subset of 62 patients had determinations of Lp(a) levels, and no significant effect of fish oil was found on this atherogenic lipoprotein.

The effect of cigarette smoking on restenosis is unexplained. A similar effect of cigarette use was observed in the TIMI-II trial.[33] In that study, the authors showed that the cigarette smokers constituted a younger group of angioplasty patients and with that difference had fewer other risk factors for coronary heart disease to which the lower restenosis rate was attributed. A similar comparison of risk factors between the smokers and nonsmokers in our study does not appear to have a similar explanation, since we did not find any striking differences in medical history and risk factors between smokers and nonsmokers, which were found by Mueller et al.[33] Of the current smokers in our study, the proportion of male and female smokers, presence of diabetes, history of myocardial infarction or angina, previous PTCA or CABG, blood pressure level, years of coronary artery disease, angina class, and mean lumen diameter at the site of angioplasty before and after PTCA did not differ significantly. Of the smokers, 16% had multiple-vessel disease compared with 28% of nonsmokers, and 38% of the latter had right coronary artery stenosis compared with 26% of the smokers. But when classified according to the most common disease locations (left circumflex coronary, left anterior descending coronary, right coronary, and other arteries), the association with smoking was not significant ($P=.22$). Only for body weight was there a significant difference ($P=.02$), as 19% of the smokers were overweight, and 25% of the nonsmokers were overweight. When these variables were included in a logistic regression, only age, previous PTCA, left anterior descending coronary artery as location of the lesion, multiple lesions, and pre-PTCA lumen diameter were significantly prognostic, but they were the same for smokers and nonsmokers. However, even if one corrected for all of these variables, smoking remained prognostic for favorable outcome from PTCA. Recently, a TIMI-4–related study[34] also reported that smokers were found to have a better outcome with thrombolysis than nonsmokers. Recurrence of ischemia was less, and mortality rates were reduced by approximately one half. Thus, there appears to be increasing evidence that some of the invasive therapies share a paradoxical better outcome for smokers than for nonsmokers. Perhaps some toxin in cigarette smoke can inhibit the proliferation of smooth muscle cells in this condition, despite the well-documented general atherogenic effect of smoking.

Although there has been much concern regarding the possibility of excessive bleeding resulting from ingestion of fish oils, no difference in clinically significant bleeding was noted despite the invasive angioplasty procedure and the fact that all patients received 325 mg/d aspirin. All bleeding times were within the normal range, but the fish oil–supplemented subjects had a small but significant increase between the value at PTCA and that at 3 months ($P<.01$).

Acknowledgments

This study was supported by grant UO1-HL-40548 from the National Institutes of Health. We thank the following for their invaluable assistance: Dr E.J. Schaefer for the Lp(a) determinations; the nurse coordinators at the collaborating centers—L. Burkert, P. Collett-Willey, J. Joseph, J. Kane, D. LeClerc, J. Noceda, and C. Melidossian; and J. Abukhalil and C. Kachoris for technical assistance.

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Inter Partes Reexamination No. 95/001,096
Declaration of Campbell Rogers, M.D.
Exhibit 92

Catheterization and Cardiovascular Interventions 70:654–660 (2007)

Randomized, Double-Blind, Multicenter Study of the Polymer-Based 17-β Estradiol-Eluting Stent for Treatment of Native Coronary Artery Lesions: Six-Month Results of the ETHOS I Trial

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Objectives: The ETHOS I trial was the first in-human experience evaluating the safety and efficacy of two different release formulations of the 17-β estradiol-eluting R-Stent™ versus uncoated control stents for the treatment of patients with single de novo native coronary lesions. **Background:** Estrogens were reported to inhibit neointimal proliferation and to accelerate endothelial regeneration after coronary angioplasty and thus could be an ideal compound to deliver on a stent for the purpose of reducing in-stent restenosis. **Methods:** Ninety-five patients were randomized to receive a slow-release ($n = 32$) or the moderate release ($n = 31$) formulations or the bare metal stent ($n = 32$). The primary end point was the 6-month percent in-stent volume obstruction by intravascular ultrasound (IVUS). **Results:** Diabetes was present in 29.5% of patients; the mean reference vessel diameter was 2.90 mm; and the mean lesion length was 13.5 mm. Primary endpoint, 6-month percent in-stent volume obstruction by IVUS, did not differ significantly between the 3 groups (31% ± 14%, 33% ± 11%, and 31% ± 14%, $P = 0.83$). Secondary endpoints also did not differ significantly between the groups including 6-month rates of in-lesion binary angiographic restenosis (13.3%, 14.3%, and 12.5%, $P = 0.90$), in-stent late loss (0.62 ± 0.49 mm, 0.66 ± 0.53 mm, and 0.84 ± 0.46 mm, $P = 0.07$), target lesion revascularization (12.5%, 6.9%, and 6.5%, $P = 0.64$), and major adverse cardiac events (18.8%, 10.3%, and 9.6%, $P = 0.31$). **Conclusions:** In this first-in-man randomized trial, the 17-β estradiol-eluting R-Stent™, in either slow- or moderate-release formulations, was well-tolerated, but showed no benefit for treatment of coronary lesions when compared to controls.

Key words: coronary artery disease; drug-eluting stents; restenosis

INTRODUCTION

The long-term efficacy of drug-eluting stents (DES) has been proved in multicenter randomized trials [1,2]. Recently, however, the safety of the first-generation DES has been questioned, mainly due to impaired healing and delayed endothelialization [3]. Estrogens have been shown to inhibit neointimal proliferation and to accelerate endothelial regeneration after coronary angioplasty [4,5]. In the EASTER (Estrogen And Stents To Eliminate Restenosis) clinical trial, the implantation of the on-site loaded 17(-Estradiol Biodiv Ysio™ stent was demonstrated to be safe and associated with low binary restenosis (6.6%) and clinical recurrence (3.3%) [6].

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Received 1 February 2007; Revision accepted 23 March 2007

DOI 10.1002/ccd.21230
Published online 11 October 2007 in Wiley InterScience (www.interscience.wiley.com).

No clinical studies have yet attempted to deliver estradiol with a local sustained release directly at the site of the obstructive atherosclerotic plaque during stenting angioplasty for the prevention of restenosis. Hypothetically, preloaded DES with different pharmacokinetics, high drug doses, and more homogeneous and programmed drug release may get better results than those observed with on-site loaded stents, designed to liberate ~50% of the total dose of estradiol in 90 min [6]. The optimization of the estradiol-eluting profile would maintain the initial burst followed by a sustained release, enabling short-term (vasodilatory) as well as longer-term (antiproliferative and re-endothelializing) actions of estradiol [7]. The purpose of the ETHOS I (estradiol eluting stents in humans for restenosis) was to provide the first in-human clinical evaluation of the safety and efficacy of the 17-β-estradiol eluting ETHOS coronary stent system (X-Cell Medical, Monmouth Junction, NJ) in a randomized, multicenter trial comparing the slow-release and moderate-release formulations with a bare-metal stent with identical platform.

MATERIALS AND METHODS

Study Design and Eligibility

This phase I, three-arm, randomized, double-blind, prospective trial was conducted at 3 centers: Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil, the Heart Center Siegburg, Siegburg and the Krankenhaus der Barmherzigen Brüder, Trier, both in Germany. The study protocol was approved by the institutional Ethics Committees at the participating centers and all patients gave written informed consent.

Eligible patients were at least 18 years old, had a diagnosis of stable angina pectoris (Canadian Cardiovascular Society 1 to 4), unstable angina pectoris (Braunwald Class IB-C, IIB-C or IIIB-C), or documented silent ischemia and were acceptable candidates for coronary artery bypass surgery. Angiographic inclusion criteria specified a single de novo lesion with stenosis >50% and <100%, length ≤18 mm, and location in a native coronary artery ≥2.5 mm and ≤3.5 mm in diameter. Exclusion criteria included women of child-bearing potential or on hormone replacement therapy, myocardial infarction within the preceding 48 hr, unprotected left main coronary disease, a total occluded vessel, a target lesion in an ostium, a bifurcation, or in a vessel with thrombus or heavy calcification, ejection fraction ≤30%, serum creatinine >2.0 mg/dl (>180 μmol/l) or baseline platelet count <100,000 cells/mm^3.

Patients were randomized in a double-blind manner to treatment with the slow-release or the moderate release formulations of the 17-β estradiol-eluting R-Stent™, or the uncoated R-Stent™ (Orbus Medical Technologies, Fort Lauderdale, FL), in a 1:1:1 ratio.

Coronary Stent Procedure

Before and after the procedure, all patients received oral aspirin (325 mg daily for 1 month, and 81 mg a day thereafter indefinitely), oral clopidogrel (300–600 mg loading dose and 75 mg once a day thereafter) or ticlopidine (500 mg), starting within 24 hr before percutaneous coronary intervention. Post-procedure treatment with oral clopidogrel or ticlopidine was continued for 2 months. During the procedure intravenous heparin was administered to maintain an activated clotting time of 250–300 sec (150–250 sec if IIb/IIIa agents were used). Lesions were treated with the use of standard interventional techniques including mandated balloon dilation before stent implantation. One stent of the assigned type was used to treat the target lesion. Additional study stents were permitted for edge dissections greater than or equal to type B or otherwise suboptimal results, and post-dilatation was at operator discretion.

In this trial a single dose of estradiol of 240 μg per 15 mm stent length was coated onto a stent for sustained local delivery to the arterial wall using either slow-release or moderate-release formulation. The inactive ingredients in the ETHOS estradiol-eluting coronary stent are parylene C and 2 nonerodable polymers: polyethylene vinyl acetate and poly n-butyl methacryiate, collectively known as the Bravo™ matrix (Surmodics, Eden Prairie, MN). The moderate and slow-release formulations are designed to liberate ~30% of the total dose of estradiol in 1 and 8 days, respectively. The remaining amount is released mostly in 30 days in both formulations. The slow-release and moderate-release 17-β estradiol-eluting R-Stent™, or the uncoated R-Stent™ were identical in appearance and available in 13, 18, and 23 mm length and diameters of 2.5, 3.0, and 3.5 mm.

Follow-Up And Core Laboratory Analysis

All the data were submitted to a data coordinating center at Cardiovascular Research Foundation, New York, NY. Follow-up clinical visits were obtained at 1 and 6 months. All clinical endpoints were adjudicated by an independent committee that was unaware of the treatment-group assignments. The patients will be evaluated at 1 and 2 years after the procedure.

Quantitative coronary angiography and intravascular ultrasound (IVUS) were obtained at the procedure, and at 6-month follow-up, and were performed at the Cardiovascular Research Foundation Core Laboratories. Quantitative coronary angiography was carried out using an automated edge-detection system (CMS, MEDIS). The reference diameter, minimum lumen diameter (MLD), and percent diameter stenosis were analyzed and measured. Measurements included the

stented segment (in-stent) as well as the lesion segment (the stented segment plus margins 5 mm proximal and distal to the stent [in-lesion]).

Stents were examined with a 40-MHz single-element mechanical IVUS transducer (ClearView, CVIS, Boston Scientific Corp.) at a pullback speed of 0.5 mm/sec. Two-dimensional and volumetric IVUS analysis was performed with the use of commercial available planimetry software (Tape Measure/Echo Plaque, Indec Systems Mountain View, CA.). Vessel, stent, lumen, and intimal hyperplasia (stent-lumen) volumes were computed for the stented segment. Percent volume obstruction (%VO) was defined as neointimal volume divided by stent volume multiplied by 100.

Study End Points and Definitions

The primary end point was the 6-month in-stent % volume obstruction by IVUS. Secondary end points included: (1) in-stent binary restenosis, late loss, diameter stenosis, and minimal lumen diameter as defined by 6-month angiography; (2) the volume of intimal hyperplasia, as defined by IVUS, at 6-month follow-up; and (3) major adverse cardiac events (MACE) including death, recurrent nonfatal myocardial infarction, emergent CABG, and/or clinically driven target vessel revascularization); target lesion revascularization; target vessel revascularization; target vessel failure and stent thrombosis in hospital, at 30 days, 6 months, 1 year, and 2 years.

Non-Q-Wave Myocardial Infarction was defined as the elevation of CK Levels to ≥3 times the upper limit of normal. Q-Wave Myocardial Infarction was defined as the development of Pathological Q-Waves in 2 or more contiguous leads associated with post-procedure CK or CK-MB levels elevated above the upper limit of normal. Binary restenosis at angiographic follow-up was defined as diameter stenosis >50%.

Stent thrombosis was classified according to the Academic Research Consortium (ARC) definitions as definite, probable, or possible [8].

Statistical Methods

The effectiveness analysis and safety evaluation were performed on an intent-to-treat basis. Thirty patients per group provided 80% power to show a reduction of in-stent volume obstruction from 30% ± 14% in the bare-metal stent arm (control) [9] to 19.8% ± 14% in the coated stent arms (a relative reduction of 34%). To detect differences between the randomized treatment assignment groups, categorical variables were compared using Fisher's exact test, and continuous variables were compared with analysis of variance. Pairwise comparisons were also made using Fisher's exact test for categorical variables and t tests for continuous variables with the Bonferroni adjustment. All tests were 2-sided with a significance level of 0.05.

RESULTS

Between August and November, 2005, 95 patients with coronary artery disease eligible for the treatment with percutaneous coronary intervention were enrolled. Baseline demographic and angiographic characteristics as well as procedural data were well matched among the groups randomly assigned to the slow-release, moderate-release or the control stent. The mean age of the patients was 62.1 ± 10.0 years, the majority were male (73.7%). Approximately one third of the patients (29.5%) had diabetes mellitus. The mean reference vessel diameter was 2.90 ± 0.40 mm and the mean lesion length was 13.46 ± 4.53 mm (Table I).

Stent length (19.5 ± 5.9, 19.8 ± 5.6, and 20.5 ± 6.0 mm) and the proportion of patients with overlapping stents did not differ significantly among the groups (6.3%, 12.9%, and 15.6%; $P = 0.48$). Rates of device success were similar (100%, 96.8%, and 93.8%; $P = 0.36$) and failure to deliver the study stent occurred in 1 patient in the moderate-release group and 2 patients in the control group. Nonstudy stents were deployed, yielding a 100% lesion and procedure success in all groups. Similar final acute gain was achieved in the 3 groups (Table II).

Angiographic follow-up was available in 94% of patients at 6 months. Primary endpoint, in-stent % volume obstruction by IVUS at 6 months, did not differ significantly among the groups (31% ± 14%, 33% ± 11% and 31% ± 14%, $P = 0.83$) (Table III). There was no aneurysm formation or late acquired malapposition in any of the groups.

Other secondary endpoints also did not differ significantly between the groups (Table IV) including 6-month rates of in-lesion binary angiographic restenosis (13.3%, 14.3%, and 12.5%, $P = 0.98$), in-stent late loss (0.82 ± 0.49 mm, 0.86 ± 0.53 mm and 0.84 ± 0.46 mm, $P = 0.97$), target lesion revascularization (12.5%, 6.9%, and 6.5%, $P = 0.64$), and target vessel revascularization (12.5%, 10.3%, and 6.5%, $P = 0.72$).

No cases of death, myocardial infarction, or repeat revascularization of the target lesion or target vessel have been observed at 30-day follow-up. Six-month MACE occurred in 6 patients treated with the slow-release stent (18.8%), 3 patients treated with the moderate-release stent (10.3%) and 2 patients treated with the control stent (6.5%) ($P = 0.31$). There was only one case of death and one case of a non-Q-wave myocardial infarction; both occurred in patients treated with the slow-release stent (Table V). Death occurred suddenly on the 5th month of follow-up, after admission

TABLE I. Baseline Clinical and Angiographic Characteristics

	Slow-release ($n = 32$)	Moderate-release ($n = 31$)	Control ($n = 32$)	P value
Age (yr)	64.1 ± 10.1	59.3 ± 10.1	62.8 ± 9.6	0.15
Male (%)	65.6	80.6	75.0	0.39
Hypertension (%)	75.0	87.1	75.0	0.40
Hyperlipidemia (%)	78.1	83.9	87.5	0.60
Current smoker (%)	15.6	22.6	28.1	0.48
Diabetes mellitus (%)	34.4	25.8	28.1	0.74
Insulin controlled	15.6	0	18.8	0.05
Oral controlled	18.8	19.4	3.1	0.10
Prior MI (%)	25.0	16.1	40.6	0.09
Prior PCI (%)	15.6	16.1	15.6	0.99
Prior CABG (%)	3.1	0	0	0.37
Unstable angina (%)	18.8	16.1	21.9	0.84
Ejection fraction (%)	63.2 ± 9.8	65.1 ± 10.9	62.1 ± 11.4	0.63
Vessel type (%)				
LAD	56.3	35.5	41.9	0.24
LCX	15.6	16.1	19.4	0.91
RCA	25.0	48.4	38.7	0.16
Ramus	3.1	0.0	0.0	0.38
Ref. diameter (mm)	2.83 ± 0.35	2.94 ± 0.40	2.92 ± 0.45	0.49
Lesion length (mm)	12.95 ± 4.23	13.86 ± 5.07	13.70 ± 4.33	0.70
Lesion MLD (mm)	0.88 ± 0.37	1.02 ± 0.35	1.12 ± 0.39	0.01
Lesion DS (%)	69.1 ± 12.1	64.8 ± 12.1	62.1 ± 13.1	0.06

CABG, coronary artery bypass surgery; DS, diameter stenosis; LAD, left anterior descending artery; LCX, left circumflex; MI, myocardial infarction; MLD, minimal luminal diameter; PCI, percutaneous coronary intervention; RCA, right coronary artery.

TABLE II. Stent Implantation and Procedural Results

	Slow-release ($n = 32$)	Moderate-release ($n = 31$)	Control ($n = 32$)	P value
Balloon predilation (%)	90.3	93.5	87.5	0.72
Number of Stents	1.09 ± 0.39	1.06 ± 0.25	1.16 ± 0.37	0.56
One (%)	93.8	93.5	84.4	0.34
Two (%)	3.1	6.5	15.6	0.18
Three (%)	3.1	0	0	0.37
Max. stent diameter (mm)	3.17 ± 0.33	3.23 ± 0.28	3.22 ± 0.31	0.74
Stent length (mm)	19.53 ± 5.87	19.83 ± 5.62	20.50 ± 5.96	0.79
Max. inflation pressure (atm)	13.85 ± 3.13	15.47 ± 2.64	13.88 ± 2.20	0.18
Use of IIb/IIIa inhibitors (%)	0	3.2	0	0.35
Final minimal diameter (mm)				
In lesion	2.31 ± 0.38	2.44 ± 0.44	2.48 ± 0.49	0.29
In stent	2.75 ± 0.34	2.85 ± 0.26	2.82 ± 0.40	0.53
Final stenosis (%)				
In lesion	19.89 ± 8.64	18.27 ± 8.41	17.08 ± 7.35	0.38
In stent	4.71 ± 7.21	4.26 ± 8.15	5.33 ± 9.38	0.88
Acute gain (mm)	1.43 ± 0.41	1.42 ± 0.57	1.36 ± 0.38	0.81

for gastrointestinal bleeding and hypotension. Intermittent episodes of chest pain occurred, with no ECG or cardiac enzymes changes, hours after endoscopic epinephrine injection for peptic ulcer treatment, ending in ventricular fibrillation that did not respond to resuscitative maneuvers. This patient has been on aspirin 100 mg/day, discontinued soon after admittance. The other patient had a non-Q-wave myocardial infarction associated with a distal lesion progression, remote from the target-lesion, which required no intervention.

According to ARC definitions, no definite or probable stent thrombosis occurred in any of the groups during the 6-month follow-up. Possible stent thrombosis, the most inclusive category, also did not differ significantly among groups (3.1%, 0, and 0, $P = 0.39$).

DISCUSSION

This study represents the first clinical experience with a polymer-based 17-β-estradiol eluting R-Stent™.

TABLE III. IVUS Measures Post-Implantation and at 6-Month Follow-Up

	Slow-release	Moderate-release	Control	*P* value
Post-Implantation:	(n = 29)	(n = 28)	(n = 28)	
Vessel (mm^2)	275.8 ± 104.7	306.2 ± 120.2	302.3 ± 125.4	0.58
Stent (mm^2)	145.4 ± 54.8	154.9 ± 70.7	147.5 ± 58.1	0.83
Lumen (mm^2)	147.3 ± 56.6	162.5 ± 67.8	149.8 ± 56.0	0.60
Min. lumen (mm^2)	6.24 ± 1.62	7.03 ± 1.89	6.43 ± 1.83	0.23
Six-month follow-up	(n = 29)	(n = 21)	(n = 27)	
Vessel (mm^2)	261.6 ± 88.5	309.6 ± 114.5	322.2 ± 95.0	0.06
Stent (mm^2)	124.7 ± 39.4	158.1 ± 55.1	159.7 ± 40.3	0.11
Lumen (mm^2)	94.4 ± 35.4	107.9 ± 45.9	109.9 ± 37.2	0.34
Min. lumen (mm^2)	3.51 ± 1.42	3.47 ± 1.47	3.94 ± 1.85	0.51
NIH (mm^2)	40.5 ± 17.1	50.6 ± 28.0	49.8 ± 24.5	0.20
%VO	31 ± 14	33 ± 11	31 ± 14	0.83

NIH, neointimal hyperplasia; %VO, percent volume obstruction.

TABLE IV. Angiographic Measures at 6 Months

	Slow-release (n = 30)	Moderate-release (n = 28)	Control (n = 31)	*P* value
MLD (mm)				
In lesion	1.81 ± 0.54	1.90 ± 0.57	1.87 ± 0.53	0.83
Proximal edge	2.53 ± 0.39	2.77 ± 0.46	2.60 ± 0.58	0.20
In stent	1.98 ± 0.57	1.97 ± 0.60	1.93 ± 0.60	0.93
Distal edge	2.26 ± 0.54	2.44 ± 0.51	2.44 ± 0.48	0.29
Stenosis (%)				
In lesion	33.9 ± 17.3	34.4 ± 16.4	35.1 ± 16.0	0.96
Proximal edge	6.4 ± 12.6	3.2 ± 12.7	9.7 ± 12.7	0.16
In stent	30.3 ± 18.7	31.8 ± 18.4	33.2 ± 18.6	0.83
Distal edge	18.1 ± 13.3	15.3 ± 12.5	15.3 ± 12.4	0.63
Late loss (mm)				
In lesion	0.51 ± 0.45	0.50 ± 0.47	0.55 ± 0.38	0.84
In stent	0.82 ± 0.49	0.86 ± 0.53	0.84 ± 0.46	0.97
Binary restenosis (%)				
In lesion	13.3	14.3	12.5	0.98
Proximal edge	0	0	0	N/A
In stent	10.0	14.3	12.5	0.98
Distal edge	3.3	0	3.2	0.62
Patterns of restenosis (%)				
Diffuse	66.7	100.0	50.0	0.16
Proliferative	33.3	0	50.0	0.35

MLD, minimal luminal diameter.

The results of the Ethos I trial showed that the estradiol-eluting coronary stent system is safe and feasible with no safety concerns related to death, myocardial infarction or stent thrombosis. There was, however, no evidence of incremental benefit associated with both formulations of the estradiol-eluting stents, compared with control, in clinical, angiographic or ultrasonographic assessments at 6-month follow-up.

Estrogen increases vasodilation, reduces the response of blood vessels to injury and prevents the development of atherosclerosis. Estrogen-induced vasodilatation appears 5–20 min after estrogen had been administered and is not dependent on modifications in gene expression; this action of estrogen is occasionally referred to as "nongenomic." This short-term vasodilatory effects of estrogen are largely mediated by the increased production of nitric oxide via cell surface receptors. Conversely, the estrogen-induced inhibition of the response to vascular injury and the preventive effect of estrogen against atherosclerosis occur over a period of hours or days after estrogen treatment and are dependent on modifications on gene expression in the vascular tissues via nuclear α and β estrogen receptors; these actions are occasionally referred to as "genomic" [7]. Specifically, 17-β-estradiol inhibits neointimal smooth muscle cell proliferation and migration [10–12] as well as

TABLE V. Clinical Outcomes at 6 Months

	Slow-release ($n = 32$)	Moderate-release ($n = 29$)	Control ($n = 32$)	*P* value
Death, *n* (%)	1 (3.1)	0	0	0.30
MI, *n* (%)	1 (3.1)	0	0	0.30
TLR, *n* (%)	4 (12.5)	2 (6.9)	2 (6.5)	0.64
TVR, *n* (%)	4 (12.5)	3 (10.3)	2 (6.5)	0.72
MACE, *n* (%)	6 (18.8)	3 (10.3)	2 (6.5)	0.31
TVF, *n* (%)	6 (18.8)	3 (10.3)	2 (6.5)	0.31

MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization.

adventitial fibroblast migration [13]. After balloon injury, estradiol attenuates the response to injury [14], promotes wound healing [15] and re-endothelialization of the vessel wall [5,16]. Also, 17-β-estradiol-coated PC stents have been shown to reduce restenosis by 40% in a porcine model [17]. An early clinical feasibility study (EASTER) conducted with on-site loaded 17β-Estradiol *BiodivYsio*™ stent provided promising data showing safety and low rates of binary restenosis (6.6%) and revascularization (3.3%) in a non-controlled selected group of patients [6]. More recently, however, Airoldi et al. showed that these on-site loaded stents were associated with a higher restenosis (23%) and revascularization (17%) rates [18].

The ETHOS I clinical design was based on prior experience with estradiol in the EASTER trial and the decision to deliver a maximum practical dose of the drug to avoid a false negative result due to insufficient dosing. Since estradiol is routinely given to patients chronically at relatively high doses, there was no increased risk to patients exposed to the dose in ETHOS I (240 μg per 13 mm stent length). Subsequent tissue uptake studies with ETHOS I stents in porcine arteries were done and showed that ETHOS I delivered far more estradiol than is required for known physiological effects, 8–10 μM on day 1 and 3 μM on day 3 (W.B. and H.S., unpublished data). Insofar as estradiol serum concentrations found in humans are typically in the 1 nM range for women and the 0.1 nM range for men, the drug dose delivered by ETHOS I stents to the arterial wall is likely to be far in excess of an effective dose. While the affinity constant (Kd) for 17-β-estradiol is 0.4 nM for both α and β receptor subtypes [19], in vitro cell culture studies have demonstrated responses to <0.1 nM estradiol [20]. Some of the actions of estradiol that are relevant to DES are likely to be multi-factorial, i.e., acting via 2 or more signaling pathways and/or receptor subtypes [7]. This type of complex activity, which is likely to be central to estradiol's effectiveness, often manifests in a "bell-shaped" response curve, whereby the desired response occurs in a relatively small dose range, and may be lost if the drug dose is either too low or too high [20–23]. Typically, the optimal dose range is about 100 nM, which is 30–100 times lower than the dose delivered in ETHOS I from day 1 to day 3. Thus, although the ETHOS I trial has provided excellent safety data, the ETHOS I stent may be less effective than a lower dose product.

A second potential reason for the lack of efficacy of estradiol is that the antirestenotic effects of estradiol may not be effective to overcome the pro-inflammatory effects of the polymer coating. In this context, estradiol could still have a role for DES, possibly associated with antiproliferative drugs, to counterbalance their negative effects on delayed endothelialization [3].

CONCLUSIONS

In this first in-man, multicenter, randomized trial, the 17-β estradiol-eluting R-Stent™ in either slow- or moderate-release formulations were well-tolerated, but showed no benefit for treatment of coronary lesions when compared to controls.

ACKNOWLEDGMENTS

The authors thank Dr. Oded Ben-Joseph, Mr. Steve Peltier, and Dr. Yen-Fang Keng for their critical review and valuable research.

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Monday Issue

SCIENTIFIC SESSION NEWS

Vol. 21, No. 6 American College of Cardiology 52nd Annual Scientific Session Chicago • March 31, 2003

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DON'T FORGET

- The Presidential Plenary Session, which includes the annual Presidential Address and Simon Dack Lecture, will be held Monday from 8 to 9 a.m. in Hall D of McCormick Place.
- The Second Annual American College of Cardiology International Lecture will be held Tuesday from 8:30 to 9:20 a.m. in Room S100 of McCormick Place.
- The 34th Annual Louis F. Bishop Lecture will be held Tuesday from 2 to 3 p.m. in the Grand Ballroom S100B of McCormick Place.
- The 52nd Annual Convocation will be held Tuesday from 6 to 8 p.m. in the Grand Ballroom of the Chicago Hilton & Towers.
- The Annual Meeting delegates session will be held Wednesday from 10:30 a.m. to 12:30 p.m. in Hall D of McCormick Place.

Drug-Eluting Stents Proven Effective *and* Cost-Efficient

Be sure to stop by ACC Central (Booth #2803) to see all of the latest products and services that the College has to offer.

Interventional cardiologists are still faced with the major problem of restenosis after successful percutaneous coronary interventions, be it balloon angioplasty or stent placement.

Based on the promising, often astounding results of earlier clinical trials, drug-eluting stents have been pegged as the leading candidate to solve—or at least greatly diminish—the problem of restenosis. Data from trials involving stents that elute sirolimus and paclitaxel—two of the most proven drugs in this area of research—were presented here on Sunday. Questions addressed by the trials were whether short-term benefits already seen with drug-eluting stents are maintained in the long-term, and whether the higher costs associated with this new technology are justified by clinical results.

Sirolimus Proves Its Cost Effectiveness Mettle

Clinical outcomes of the SIRIUS trial, reported in October 2002, showed that patients receiving the Cypher sirolimus-eluting stents had a significant reduction in risk of death, heart attack, or repeat stenting or bypass surgery of the same artery.

Now there are data showing that clinical benefits of the sirolimus-coated stent may justify its initial extra expense, at least over the first year. A presentation Sunday described a pharmacoeconomic substudy of SIRIUS.

Drug-eluting stents, when they become commercially available, will cost an estimated $2,000 more than standard metal stents, said David J. Cohen, MD, Beth Israel-Deaconess Medical Center, Boston, in a press conference here Sunday.

But the cost is matched by a savings of more than $2,000 in the first year after implant, related to the reduction in number of revascularizations, Dr. Cohen said.

See DRUG-ELUTING STENTS, page 7

Folate Therapy Increases Restenosis Rates in Stent Recipients

Contrary to findings from previous studies, administration of folate and other B vitamins to patients receiving coronary stents does not lower the risk of restenosis, according to the results of a randomized, controlled study presented on Sunday. Instead, the trial results suggest that such vitamin therapy can actually increase that risk over the six months following the stent procedure.

The Folate After Coronary Intervention (FACIT) trial enrolled 636 patients who underwent successful coronary stenting and were randomly assigned to receive or not receive supplemental treatment with folate and vitamins B6 and B12. The trial explored whether folate—which has been shown to reduce elevated blood levels of homocysteine—can limit in-stent restenosis during the six months following their implantation.

Based on the previously published Swiss Heart Study, which suggested that folate therapy could reduce the restenosis rate by as much as 50 percent, "some interventionalists already began giving folate to prevent restenosis," said Helmut W. Lange, MD, Heart Center Bremen, Kardiologische Praxis, Bremen, Germany.

"The results of FACIT are surprisingly contradictory of its hypothesis as well as of the published results of the Swiss Heart Study, in that folate therapy led to a significantly smaller minimum lumen diameter at the six-month follow-up, as well as higher restenosis and major adverse cardiac event rates," Dr. Lange said. The increased restenosis risk, he added, occurred despite significantly lower homocysteine levels in the folate-treated patients."

The folate, B6, B12 vitamin combination, he concluded, should be avoided following coronary stent implantation.

Dr. Lange added that, while it is currently being studied, at this time no conclusions can be drawn on the efficacy of folate for the secondary prevention of adverse events in patients with chronic CAD.

"This is one of the few studies I have ever found that tells us that vitamins are not always good for us, that they can even be harmful in certain settings," Dr. Lange said.

OCTOPUS: Stenting Recommended as First Choice of Revascularization in Single-Vessel Coronary Disease

Despite hopes that a contemporary reduced-risk technique for coronary artery bypass surgery would prove a better option in most patients scheduled to receive coronary stents, a randomized trial suggests stents may be preferable.

In the OCTOPUS trial, 280 patients with mostly single-vessel coronary disease were randomly assigned to receive a stent or "beating heart" or "off-pump" bypass surgery. Studies have shown that beating-heart surgery can avoid the increased risks, time, and costs of conventional CABG using a cardiopulmonary bypass.

Patients in the two groups showed statistically similar one-year rates of event-free survival and freedom from cardiac chest pain (96 percent for stenting, 94 percent for CABG), according to Peter de Jaegere, MD, University Medical Center, Utrecht, the Netherlands. However, coronary stenting was associated with significantly shorter hospital stays and lower overall costs.

"The PTCA is so minimally invasive, it was performed on an outpatient basis, so the difference in number of days' hospital stay was quite large," Dr. de Jaegere said during a Sunday morning news conference.

"Ultimately, our primary concern was safety and efficacy, the two things that matter most to the patients," Dr. de Jaegere said. "They want to be able to go home and not have to see the doctor again."

The combination of little or no difference in cardiac outcomes and quality of life and the greater cost-effectiveness of stenting, said Dr. de Jaegere, indicates that it should be recommended as the first choice of revascularization for the kind of patients entered into the OCTOPUS study.

Preview New Quality CathKIT at ACC Central

While at ACC '03, be sure and visit ACC Central (Booth #2003) to examine a new interactive, Web-based resource called CathKIT, designed to help cardiac catheterization laboratories improve the quality of their systems, processes, and patient outcomes.

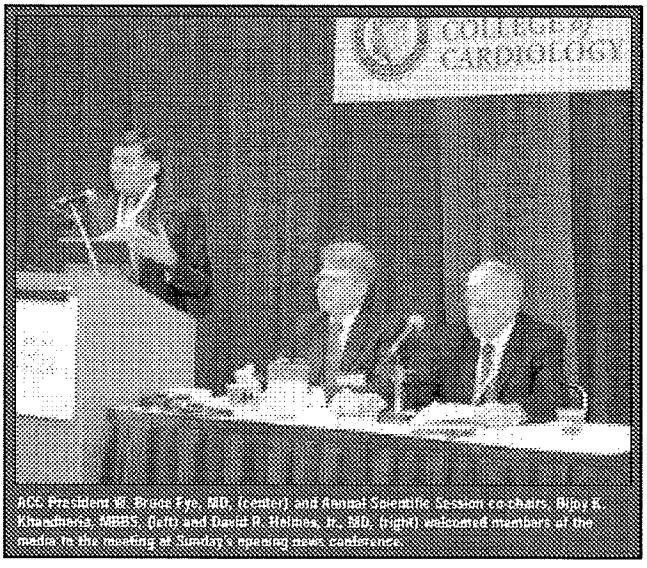
The foundation of CathKIT is derived from recommendations in ACC/American Heart Association (AHA) practice guidelines and expert consensus documents that all cardiac catheterization laboratories implement a continuous quality improvement (CQI) process. CathKIT provides a framework to address quality at many different levels. CathKIT is a joint effort of the College and the Society for Cardiac Angiography and Interventions (SCA&I).

Users will find information on all of the traditional measures of quality, such as complication rates and radiation exposure, as well as training standards, credentialing, scheduling efficiency, and patient flow.

Feedback from physicians and cardiac catheterization laboratory staff is essential to ensure the usefulness of CathKIT, which is being pilot-tested through this summer and will be released in the fall.

ACC-NCDR™ Pilots New Web Portal at ACC Central

CathKIT is designed to be a stand-alone product, but it also complements the ACC-National Cardiovascular Data Registry™ (ACC-NCDR™). At ACC '03, the NCDR™ will unveil its latest advance—a demonstration version of a new Web portal that will make it easy for Registry participants to update their profiles and obtain reports.



ACC President W. Bruce Fye, MD (center) and Annual Scientific Session co-chairs Vijay K. Kapadvanj, MBBS, Delhi and David R. Holmes, Jr., MD, (right) welcomed members of the media to the meeting at Sunday's opening news conference.

Meeting Reminders

Registration

The ACC '03 registration area is located in Hall A of McCormick Place South and is open during the following hours:

Monday .....7 a.m. – 5 p.m.
Tuesday .....7:30 a.m. – 5 p.m.
Wednesday .....8 a.m. – noon

ACC Office

The ACC Office is located in Room S501 of McCormick Place South. Telephone: 312-791-6737; fax: 312-791-6735. ACC staff are available to help you during the following hours:

Monday .....7:30 a.m. – 5:30 p.m.
Tuesday.....7:30 a.m. – 5:30 p.m.
Wednesday.....8 a.m. – Noon

ACC Gala Dinner

Always a highlight of the Annual Scientific Session, the ACC Gala Dinner will be held Tuesday from 8:30 to 11:30 p.m. Guests will be able to choose where they sit when they arrive at the event. No advance seating assignments will be made, with the exception of the president's tables. Each table will seat 10 guests and will be filled on a first-come, first-served basis. If you would like to sit with certain people, arrive early to hold the table for your group.

Questions can be posed at the ACC Gala Dinner Desk, located in the Grand Concourse of McCormick Place.

Shuttle Service

Complimentary shuttle service will operate daily from McCormick Place and the official hotels of the Annual Scientific Session. Check the shuttle sign posted in the lobby of each hotel for additional information, changes, frequency of service, and specific departure times for the designated route. General hours of operation are as follows:

Monday .....6:30 a.m. – 6:30 p.m.
Tuesday.....6:30 a.m. – 6:30 p.m.
Wednesday.....6:30 a.m. – 1 p.m.

The scheduled end times are when the last shuttles will depart from McCormick Place. The last shuttles will depart from hotels approximately 90 minutes before this time.

Audiotapes/Audio-CDs

Audiotapes and audio-CDs of selected sessions will be available two hours after each session concludes and may be purchased at Audiotape Sales, located in the Hall D foyer of McCormick Place (East/Lakeside building). Hours of operation are as follows:

Monday .....8 a.m. – 7 p.m.
Tuesday.....8 a.m. – 8 p.m.
Wednesday .....7 a.m. – 4 p.m.

Name Badges

Your badge serves as your passport to education sessions, the Exposition, and complimentary shuttle service. Attendees must wear their name badge at all times. ACC security will not allow people without badges to attend events. For your safety, we recommend that you do not wear your name badge after leaving the convention center.

Locator System

The Locator System kiosks will allow attendees to search for other attendees, exhibiting companies, and products. The system includes a computerized ACC '03 Exposition layout. Attendees may also send and retrieve messages using this system. These kiosks are located in the registration area (McCormick Place South, Hall A) and the Hall D foyer (McCormick Place East/Lakeside building).

Restaurant Reservations

The ACC '03 Restaurant Reservation Service booth is located in the Grand Concourse of McCormick Place during the following hours:

Monday .....9 a.m. – 5 p.m.
Tuesday.....9 a.m. – 5 p.m.

The restaurant reservation service is also available by calling 312-791-6746.

ACC Central

McCormick Place, South Building, Hall A

UNLOCK Your ACC '03 Experience at ACC Central, Booth #2003

New hours

Saturday, March 29, 12 p.m.–5 p.m.
Sunday, March 30, 9 a.m.–5 p.m.
Monday, March 31, 9 a.m.–5 p.m.
Tuesday, April 1, 9 a.m.–5 p.m.

Here are the tools you need to support your clinical practice. Find the latest technology and plentiful resources to enhance and distinguish the quality of patient care you provide. Discover valuable presentations, new products, special services, and demonstrations that complement all your professional interests.

ACC Central has them all:

Advocacy—Get news about current advocacy activities on behalf of your profession, reimbursement issues, and other issues of concern to cardiovascular specialists.

Quality—Use the beaming stations to download ACC/AHA Practice Guidelines, learn about the enrollment benefits of NCDR™ and GAP (Guidelines in Practice) activities, and view demonstrations of the CathKIT rolling out soon for cath lab personnel.

ACCF CME Programs—Register for ACCF Board Review and Learning Center programs at Heart House, in Seattle, and Chicago. Look at the year's schedule of programs, see the full spectrum of topics offered, and learn more about Internet opportunities for learning. Take a virtual tour of the new ACCF Blended Learning Community.

Educational Products—Use a demonstration monitor to try one of the ACCF's many stellar Self-Assessment Programs: the new ACCSAP V, CathSAP II, ECG-SAP I, II, and III, the new EchoSAP IV, and EPSAP II. Meet SAP editors from 11 a.m.–1 p.m., daily. Save 20 percent on all ACCF products, including ACCEL, throughout ACC '03.

Cardiosource—A main attraction at ACC Central, this all-inclusive, one-stop, cardiology portal challenges your intellect and fans your professional imagination. Bring a colleague to test-drive one of the Cardiosource interactive demonstration stations and save 20 percent on a premium access subscription when you sign up at ACC '03.

Membership—Check out your iMIS listing to see if your CME credits are current. Pay your membership dues, or just say hello to the ACC staff on duty at the booth.

Webcast Stations—Download the ACC '03 e-Program to your handheld device and later access need-to-know information about sessions, shuttle service, hotels, exhibitors, and ACC on-site offices. Put together your customized ACC '03 schedule using the online program planner.

Emblem Products—Choose a souvenir for your favorite staff back home, your practice partner, or treat yourself to a paperweight for your desk.

Charitable Giving—Learn more about the goals and projects of your professional association. Pick up the new ACCF Guide to Giving and learn what you and the ACC Foundation can accomplish together.

ACC 03

52nd Annual Scientific Session
March 30–April 2
Chicago

The mission of the American College of Cardiology is to foster optimal cardiovascular care and heart health through advocacy, education, promotion of research, leadership in the development of standards and guidelines, and the dissemination of cardiovascular policy.